PATENT
Attorney Docket No. AMI-087-R

GLYCOPEPTIDE DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICAITONS

This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 60/___,___, which was converted into a provisional application pursuant to 37 C.F.R. § 1.53(c)(2) from U.S. Patent Application No. 09/499,081, filed February 4, 2000; the disclosure of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to novel derivatives of glycopeptide antibiotics. This invention also relates to pharmaceutical compositions containing such glycopeptide derivatives; to methods of using such glycopeptide derivatives as antibacterial agents; and to processes and intermediates for preparing such glycopeptide derivatives.

Background

Glycopeptides (dalbaheptides) are a well-known class of antibiotics produced by various microorganisms. These complex multi-ring peptide compounds are effective antibacterial agents against a majority of Gram-positive bacteria. The use of glycopeptides as antibiotics, however, has been overshadowed by the semi-synthetic penicillins, cephalosporins and lincomycin due to the higher levels of mammalian toxicity observed for some glycopeptides. In recent years, however, bacteria resistant to the penicillins, cephalosporins and the like have emerged resulting in, for example, multiple-resistant and methicillin-resistant staphylococcal (MRS) infections. Glycopeptides, such as vancomycin, are typically effective against such microorganisms and, as a result, vancomycin has become the drug of last resort for MRS and other infections. The glycopeptides are believed to be effective against such resistant microorganism because their mode of action is

different from other antibiotics. In particular, the glycopeptides are believed to selectively inhibit a different step in bacterial cell wall synthesis compared to penicillin-type antibiotics.

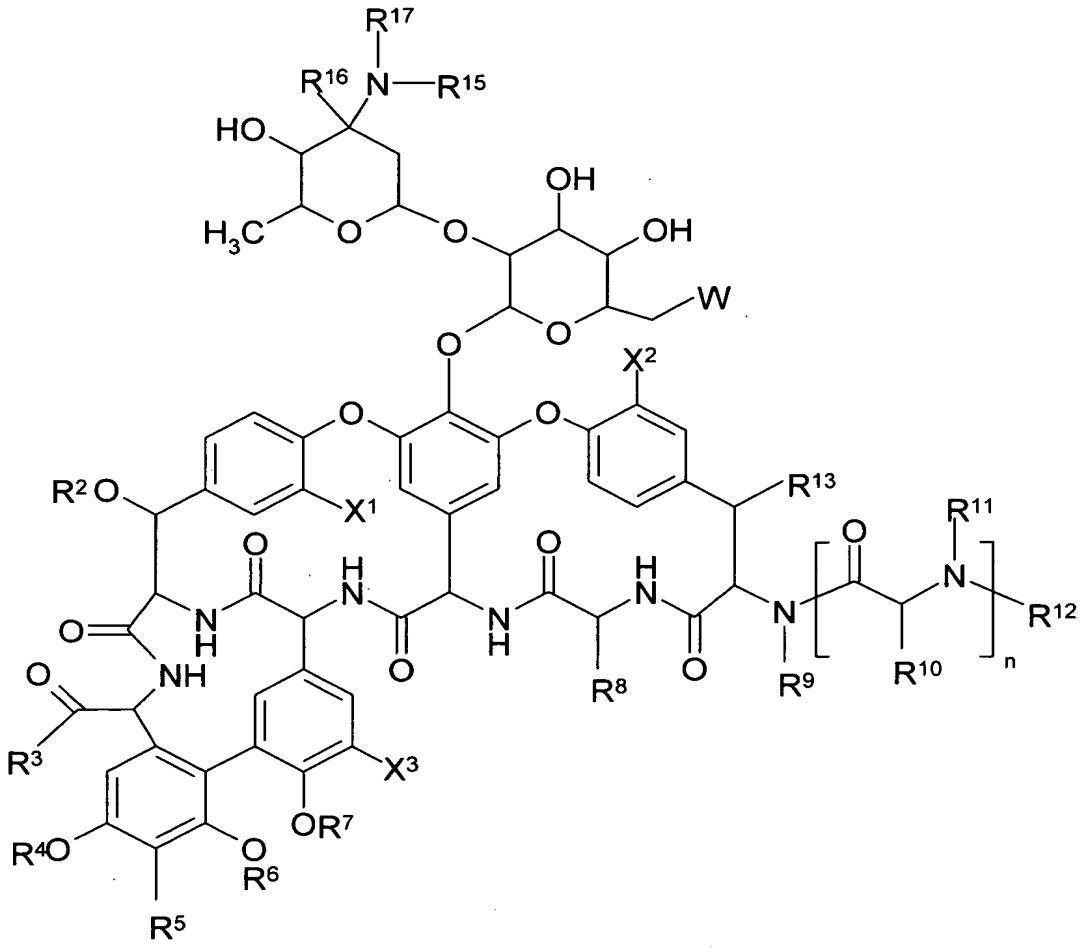
A number of derivatives of vancomycin and other glycopeptides are known in the art. For example, see U.S. Patent Nos. 4.639,433; 4,643,987; 4,698,327; 4,914,187; 5,591,714; 5,750,509; 5,840,684; 5,843,889; 5,916,873; 5,919,756; 5,952,310; 5,977,062; and 5,977,063. Other derivatives are disclosed in EP 0 182 157; EP 0 351 597; EP 0 376 041; EP 0 460 448; EP 0 525 499; WO 88/06600; WO 90/11300; WO 97/40067; WO 98/52592; WO 99/42476; WO 99/56760; WO 00/04044; and in Russian Journal of Bioorganic Chemistry, 24(9), 570-587 (1998). The disclosures of these and other documents referred to throughout this application are incorporated herein by reference in their entirety.

A need still exists, however, for novel glycopeptide derivatives having antibacterial properties, preferably having enhanced activity, improved selectivity and reduced mammalian toxicity. Moreover, since certain microorganisms are beginning to develop resistance to vancomycin, it would be highly desirable to provide novel glycopeptide derivatives which are effective against a broad spectrum of bacteria, including vancomycin resistant strains of bacteria.

SUMMARY OF THE INVENTION

The present invention provides novel derivatives of glycopeptide antibiotics having antibacterial activity. Among other properties, compounds of this invention may have enhanced activity, improved selectivity and/or reduced mammalian toxicity compared to the corresponding underivatized glycopeptide.

Accordingly, in one of its composition aspects, this invention provides a compound of formula I:



I

wherein

R^2 is hydrogen or a saccharide group optionally substituted with $-R^a-Y-R^b-(Z)_x$;

R^3 is $-OR^c$, $-NR^cR^c$, $-O-R^a-Y-R^b-(Z)_x$, $-NR^c-R^a-Y-R^b-(Z)_x$, $-NR^cR^e$, or $-O-R^e$;

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $-R^a-Y-R^b-(Z)_x$, $-C(O)R^d$ and a saccharide group optionally substituted with $-R^a-Y-R^b-(Z)_x$;

R^5 is selected from the group consisting of hydrogen, halo, $-CH(R^c)-NR^cR^c$, $-CH(R^c)-NR^cR^e$ and $-CH(R^c)-NR^c-R^a-Y-R^b-(Z)_x$;

R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $-R^a-Y-R^b-(Z)_x$, $-C(O)R^d$ and a saccharide group optionally substituted with $-NR^c-R^a-Y-R^b-(Z)_x$, or R^5 and R^6 can be joined, together with the atoms to which they are attached, form a heterocyclic ring optionally substituted with $-NR^c-R^a-Y-R^b-(Z)_x$;

R^7 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $-R^a-Y-R^b-(Z)_x$, and $-C(O)R^d$;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^9 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^{10} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic; or R^8 and R^{10} are joined to form $-Ar^1-O-Ar^2-$, where Ar^1 and Ar^2 are independently arylene or heteroarylene;

R^{11} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic, or R^{10} and R^{11} are joined, together with the carbon and nitrogen atoms to which they are attached, to form a heterocyclic ring;

R^{12} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, $-C(O)R^d$, $-C(NH)R^d$, $-C(O)NR^cR^c$, $-C(O)OR^d$, $-C(NH)NR^cR^c$ and

$-R^a-Y-R^b-(Z)_x$, or R^{11} and R^{12} are joined, together with the nitrogen atom to which they are attached, to form a heterocyclic ring;

R^{13} is selected from the group consisting of hydrogen or $-OR^{14}$;

R^{14} is selected from hydrogen, $-C(O)R^d$ and a saccharide group;

R^{15} is hydrogen or $-R^a-Y-R^b-(Z)_x$;

R^{16} is hydrogen or methyl;

R^{17} is hydrogen, alkyl or substituted alkyl;

each R^a is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

each R^b is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene, provided R^b is not a covalent bond when Z is hydrogen;

each R^c is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $-C(O)R^d$;

each R^d is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^e is a saccharide group;

W is selected from the group consisting of $-OR^c$, $-SR^c$, $-S-S-R^d$, $-NR^cR^c$, $-S(O)R^d$, $-SO_2R^d$, $-NR^cC(O)R^d$, $-OSO_2R^d$, $-OC(O)R^d$, $-NR^cSO_2R^d$, $-C(O)NR^cR^c$, $-C(O)OR^c$, $-C(NR^c)OR^c$, $-SO_2NR^cR^c$, $-SO_2OR^c$, $-P(O)(OR^c)_2$, $-P(O)(OR^c)NR^cR^c$, $-OP(O)(OR^c)_2$, $-OP(O)(OR^c)NR^cR^c$, $-OC(O)OR^d$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^c$, $-OC(O)NR^cR^c$, $-NR^cSO_2NR^cR^c$; $-N^+(R^c)=CR^cR^c$, $-N=P(R^d)_3$, $-N^+(R^d)_3$, $-P^+(R^d)_3$, $-C(S)OR^d$, and $-C(S)SR^d$;

X^1, X^2 and X^3 are independently selected from hydrogen or chloro;

each Y is independently selected from the group consisting of oxygen, sulfur, -S-S-, $-NR^c-$, -S(O)-, $-SO_2-$, $-NR^cC(O)-$, $-OSO_2-$, $-OC(O)-$, $-NR^cSO_2-$, $-C(O)NR^c-$, $-C(O)O-$, $-SO_2NR^c-$, $-SO_2O-$, $-P(O)(OR^c)O-$, $-P(O)(OR^c)NR^c-$, $-OP(O)(OR^c)O-$, $-OP(O)(OR^c)NR^c-$, $-OC(O)O-$, $-NR^cC(O)O-$, $-NR^cC(O)NR^c-$, $-OC(O)NR^c-$ and $-NR^cSO_2NR^c-$;

each *Z* is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic;

n is 0, 1 or 2;

x is 1 or 2;

and pharmaceutically acceptable salts, stereoisomers and prodrugs thereof;

provided that at least one of R^{15}, R^2, R^3, R^4, R^5, R^6, R^7 or R^{12} has a substitutent of the formula $-R^a-Y-R^b-(Z)_x$;

and further provided that:

(i) when Y is $-NR^c-$, R^c is alkyl of 1 to 4 carbon atoms, Z is hydrogen and R^b is alkylene, then R^b contains at least 5 carbon atoms;

(ii) when Y is $-C(O)NR^c-$, Z is hydrogen and R^b is alkylene, then R^b contains at least 5 carbon atoms;

(iii) when Y is sulfur, Z is hydrogen and R^b is alkylene, then R^b contains at least 7 carbon atoms; and

(iv) when Y is oxygen, Z is hydrogen and R^b is alkylene, then R^b contains at least 11 carbon atoms.

In the compounds of formula I, R^2 is preferably hydrogen.

R^3 is preferably $-OR^c$ or $-NR^cR^c$; more preferably R^3 is -OH. Particularly preferred R^3 groups are those shown in Tables I-IV as R^{22}.

Preferably, R^4, R^6 and R^7 are each independently selected from hydrogen or $-C(O)R^d$. More preferably, R^4, R^6 and R^7 are each hydrogen.

R^5 is preferably hydrogen, $-CH_2-NHR^c$, $-CH_2-NR^cR^e$ and $-CH_2-NH-R^a-Y-R^b-(Z)_x$, where R^a, R^b, R^c, R^e, Y, *Z* and *x* are as defined herein. Particularly preferred R^5 groups include:

hydrogen;

-CH_2-*N*-(*N*-CH_3-D-glucamine);

-CH_2-NH-CH_2CH_2-NH-$(CH_2)_9CH_3$;

-CH_2-NH-CH_2CH_2-NH-$(CH_2)_{11}CH_3$;

-CH_2-NH-$(CH_2)_5$-COOH; and

-CH_2-*N*-(2-amino-2-deoxygluconic acid).

In one embodiment, R^5 is preferably hydrogen. Other preferred R^5 groups are those shown in Table III as R^{23}.

Preferably, R^8 is -$CH_2C(O)NH_2$, -CH_2COOH, benzyl, 4-hydroxyphenyl or 3-chloro-4-hydroxyphenyl. More preferably, R^8 is -$CH_2C(O)NH_2$.

R^9 is preferably hydrogen or alkyl. More preferably, R^9 is hydrogen.

R^{10} is preferably alkyl or substituted alkyl. More preferably, R^{10} is the side-chain of a naturally occurring amino acid. Still more preferably, R^{10} is isobutyl.

R^{11} is preferably hydrogen or alkyl. More preferably, R^{11} is hydrogen or methyl. Still more preferably, R^{11} is methyl.

R^{12} is preferably hydrogen, alkyl, substituted alkyl or $-C(O)R^d$. More preferably, R^{12} is hydrogen or -CH_2COOH. Still more preferably, R^{12} is hydrogen. Other preferred R^{12} groups are those shown in Table II as R^{27}.

R^{13} is preferably -OR^{14} where R^{14} is hydrogen, i.e, R^{13} is preferably -OH.

R^{15} is preferably $-R^a-Y-R^b-(Z)_x$, where R^a, R^b, R^c, R^e, Y, *Z* and *x* are as defined herein;

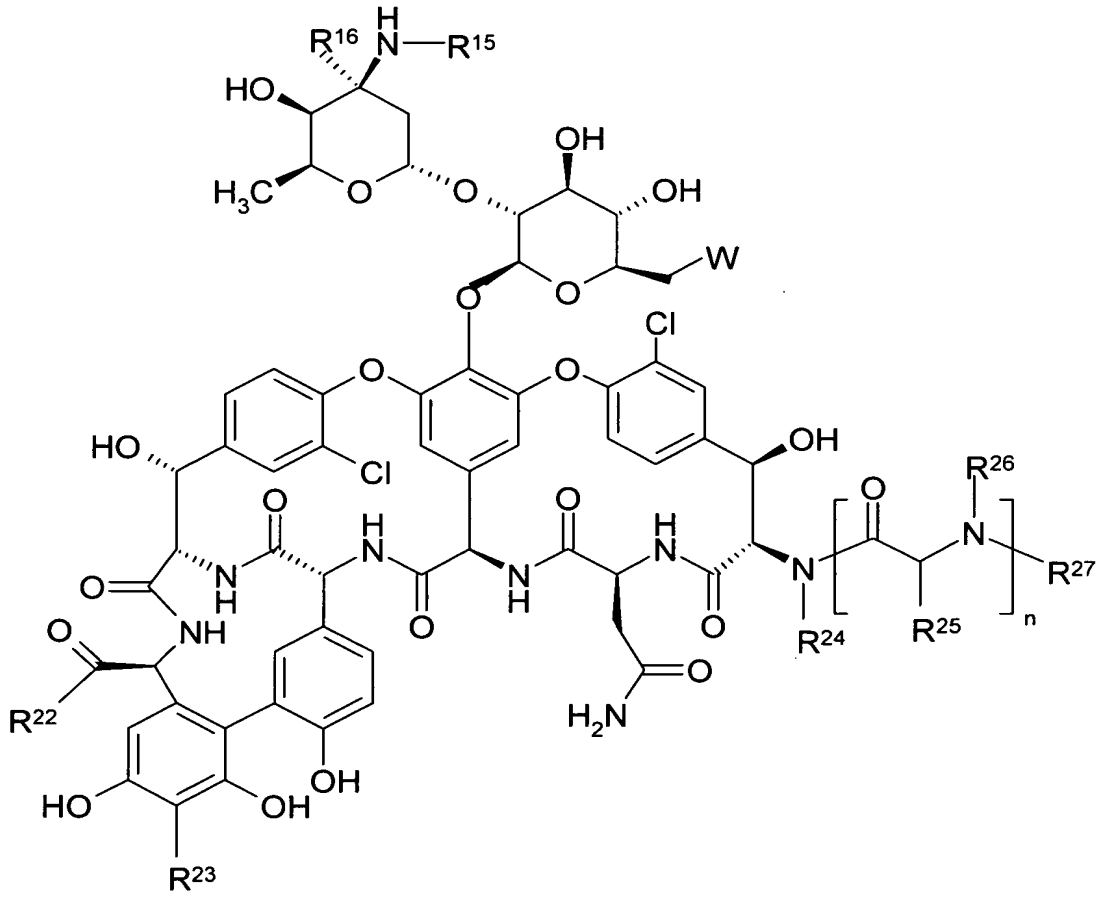
R^{16} is preferably methyl;

R^{17} is preferably hydrogen;

X^1 and X^2 are preferably chloro. X^3 is preferably hydrogen.

In a preferred embodiment of the compounds of formula I, R^2, R^4, R^5, R^6, R^7, R^9, R^{12} and R^{17} are hydrogen; R^3 and R^{13} are -OH; R^8 is -$CH_2C(O)NH_2$; R^{10} is isobutyl; R^{11} and R^{16} are methyl; R^{15} is $-R^a-Y-R^b-(Z)_x$; X^1 and X^2 are chloro; X^3 is hydrogen; and *n* is 1.

In still another of its composition aspects, this invention provides a compound of formula II:



II

wherein

R^{15} is hydrogen or $-R^a-Y-R^b-(Z)_x$;

R^{16} is hydrogen or methyl;

R^{22} is $-OR^c$, $-NR^cR^c$, $-O-R^a-Y-R^b-(Z)_x$ or $-NR^c-R^a-Y-R^b-(Z)_x$;

R^{23} is selected from the group consisting of hydrogen, halo, $-CH(R^c)-NR^cR^c$, $-CH(R^c)-R^e$ and $-CH(R^c)-NR^c-R^a-Y-R^b-(Z)_x$;

R^{24} is selected from the group consisting of hydrogen and lower alkyl;

R^{25} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl,

substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^{26} is selected from the group consisting of hydrogen and lower alkyl; or R^{25} and R^{26} are joined, together with the carbon and nitrogen atoms to which they are attached, to form a heterocyclic ring;

R^{27} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, $-C(O)R^d$, $-C(NH)R^d$, $-C(O)NR^cR^c$, $-C(O)OR^d$, $-C(NH)NR^cR^c$ and $-R^a-Y-R^b-(Z)_x$, or R^{26} and R^{27} are joined, together with the nitrogen atom to which they are attached, to form a heterocyclic ring;

each R^a is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

each R^b is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene, provided R^b is not a covalent bond when Z is hydrogen;

each R^c is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $-C(O)R^d$;

each R^d is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^e is an aminosaccharide group;

W is selected from the group consisting of $-OR^c$, $-SR^c$, $-S-S-R^d$, $-NR^cR^c$, $-S(O)R^d$, $-SO_2R^d$, $-NR^cC(O)R^d$, $-OSO_2R^d$, $-OC(O)R^d$, $-NR^cSO_2R^d$, $-C(O)NR^cR^c$, $-C(O)OR^c$, $-C(NR^c)OR^c$, $-SO_2NR^cR^c$, $-SO_2OR^c$, $-P(O)(OR^c)_2$, $-P(O)(OR^c)NR^cR^c$, $-OP(O)(OR^c)_2$, $-OP(O)(OR^c)NR^cR^c$, $-OC(O)OR^d$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^c$,

$-OC(O)NR^cR^c$, $-NR^cSO_2NR^cR^c$; $-N^+(R^c)=CR^cR^c$, $-N=P(R^d)_3$, $-N^+(R^d)_3$, $-P^+(R^d)_3$, $-C(S)OR^d$, and $-C(S)SR^d$;

each Y is independently selected from the group consisting of oxygen, sulfur, $-S-S-$, $-NR^c-$, $-S(O)-$, $-SO_2-$, $-NR^cC(O)-$, $-OSO_2-$, $-OC(O)-$, $-NR^cSO_2-$, $-C(O)NR^c-$, $-C(O)O-$, $-SO_2NR^c-$, $-SO_2O-$, $-P(O)(OR^c)O-$, $-P(O)(OR^c)NR^c-$, $-OP(O)(OR^c)O-$, $-OP(O)(OR^c)NR^c-$, $-OC(O)O-$, $-NR^cC(O)O-$, $-NR^cC(O)NR^c-$, $-OC(O)NR^c-$ and $-NR^cSO_2NR^c-$;

each *Z* is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic;

n is 0, 1 or 2;

x is 1 or 2;

and pharmaceutically acceptable salts, stereoisomers and prodrugs thereof;

provided that at least one of R^{15}, R^{22}, R^{23} or R^{27} has a substitutent of the formula $-R^a-Y-R^b-(Z)_x$;

and further provided that:

(i) when Y is $-NR^c-$, R^c is alkyl of 1 to 4 carbon atoms, Z is hydrogen and R^b is alkylene, then R^b contains at least 5 carbon atoms;

(ii) when Y is $-C(O)NR^c-$, Z is hydrogen and R^b is alkylene, then R^b contains at least 5 carbon atoms;

(iii) when Y is sulfur, Z is hydrogen and R^b is alkylene, then R^b contains at least 7 carbon atoms; and

(iv) when Y is oxygen, Z is hydrogen and R^b is alkylene, then R^b contains at least 11 carbon atoms.

In the compounds of formula II, R^{15} is preferably $-R^a-Y-R^b-(Z)_x$, where R^a, R^b, R^c, R^e, Y, *Z* and *x* are as defined herein.

R^{16} is preferably methyl.

R^{22} is preferably $-OR^c$ or $-NR^cR^c$; more preferably R^{22} is -OH. Particularly preferred R^{22} groups are those shown in Tables I-IV.

R^{23} is preferably hydrogen, $-CH_2-R^e$, $-CH_2-NHR^c$ and $-CH_2-NH-R^a-Y-R^b-(Z)_x$. Particularly preferred R^{23} groups include:

hydrogen;

$-CH_2$-*N*-(*N*-CH_3-D-glucamine);

$-CH_2-NH-CH_2CH_2-NH-(CH_2)_9CH_3$;

$-CH_2-NH-CH_2CH_2-NH-(CH_2)_{11}CH_3$;

$-CH_2-NH-(CH_2)_5-COOH$; and

$-CH_2$-*N*-(2-amino-2-deoxygluconic acid).

In one preferred embodiment, R^{23} is hydrogen. Other preferred R^{23} groups are shown in Table III.

R^{24} is preferably hydrogen or alkyl. More preferably, R^{24} is hydrogen.

R^{25} is preferably alkyl or substituted alkyl. More preferably, R^{25} is the side-chain of a naturally occurring amino acid. Still more preferably, R^{25} is isobutyl.

R^{26} is preferably hydrogen or alkyl. More preferably, R^{26} is hydrogen or methyl. Still more preferably, R^{26} is methyl.

R^{27} is preferably hydrogen, alkyl, substituted alkyl or $-C(O)R^d$. More preferably, R^{27} is hydrogen or $-CH_2COOH$. Still more preferably, R^{27} is hydrogen. Other preferred R^{27} groups are those shown in Table II.

In a preferred embodiment of the compounds of formula II, R^{15} is $-R^a-Y-R^b-(Z)_x$; R^{16} and R^{26} are methyl; R^{22} is -OH; R^{23}, R^{24} and R^{27} are hydrogen; R^{25} is isobutyl; and *n* is 1.

In a preferred embodiment of the compounds of this invention, *W* is selected from the group consisting of $-NR^cR^c$, $-NR^cC(O)R^d$, $-NR^cSO_2R^d$, $-NR^cC(O)OR^d$, $-NR^cC(O)NR^cR^c$ and $-NR^cSO_2NR^cR^c$. More preferably, *W* is $-NR^cR^c$ or $-NR^cC(O)R^d$. Still more preferably, *W* is $-NR^cR^c$.

In another preferred embodiment, *W* is selected from the group consisting of:

$-N_3$,

$-NH_2$,

$-NHNH_2$,

$-NHC(O)CF_3$,

$-NHC(O)CH_2NH_2$,

$-NHC(S)NHCH_3$,

-$SCH(CH_3)_2$,

-SCH_2COOH,

-$NH(CH_2)_9CH_3$,

-$NHC(O)(CH_2)_{12}CH_3$,

imidazol-1-yl,

-S-(1-CH_3-tetrazol-5-yl),

-S-(3-H_2N-1,2,4-triazol-5-yl),

-S-(5-H_2N-1,3,4-thiadiazol-2-yl),

-S-(3-H_2NNH-4-H_2N-1,2,4-triazol-5-yl),

-NHC(O)-(thiophen-2-yl),

-S-(phenyl),

-S-(4-Br-phenyl),

-S-(3-Cl-phenyl),

-S-(4-CF_3-pyrimidin-2-yl),

-S-(4-H_2N-pyrimidin-2-yl),

-S-(4,6-di-H_2N-pyrimidin-2-yl),

-S-(4-HO-6-H_2N-pyrimidin-2-yl),

-S-(4-HO-6-CH_3-pyrimidin-2-yl),

-S-(6-azathymin-2-yl),

-$NHCH_2$-(2-HO-5-Cl-phenyl),

-NHC(O)-(2-I-phenyl),

-$S(O)_2$-(2,4,6-tri-CH_3-phenyl),

-S-(5-CH_3O-benzimidazol-2-yl),

-S-(5-Cl-benzimidazol-2-yl),

-NHC(O)-(quinoxalin-2-yl),

-$NHCH_2$-[4-(4-Cl-phenyl)phenyl],

-NHC(O)-[4-(4-Cl-phenyl)phenyl],

-$NHCH_2$-[5-(4-Cl-phenyl)furan-2-yl],

-S-(5-phenyl-1,3,4-oxadiazol-2-yl),

-S-[1-(4-HO-phenyl-)tetrazol-5-yl],

-S-(4,5-diphenyloxazol-2-yl), and

$-OS(O)_2$-(pyren-2-yl).

More preferably, *W* is $-NH_2$.

Each R^a is preferably independently selected from alkylene having from 1 to 10 carbon atoms, more preferably, from 1 to 6 carbon atoms. In a preferred embodiment, R^a is ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$) or butylene ($-CH_2CH_2CH_2CH_2-$). Still more preferably, R^a is ethylene or propylene.

When Z is hydrogen, R^b is preferably alkylene of from 8 to 12 carbon atoms. Accordingly, in this embodiment, R^b and Z preferably form an *n*-octyl, *n*-nonyl, *n*-decyl, *n*-undecyl or *n*-dodecyl group. When Z is other than hydrogen, R^b is preferably alkylene of from 1 to 10 carbon atoms. In this embodiment, R^b is preferably methylene, $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_8-$, $-(CH_2)_9-$ or $-(CH_2)_{10}-$.

Each Y is preferably independently selected from the group consisting of oxygen, sulfur, -S-S-, $-NR^c-$, $-S(O)-$, $-SO_2-$, $-NR^cC(O)-$, $-OC(O)-$, $-NR^cSO_2-$, $-C(O)NR^c-$, $-C(O)O-$ and $-SO_2NR^c-$. More preferably, Y is oxygen, sulfur, $-NR^c-$ or $-NR^cSO_2-$. Still more preferably, Y is -NH- or sulfur.

Preferably, each *Z* is independently selected from hydrogen, aryl, cycloalkyl, heteroaryl and heterocyclic. More preferably, *Z* is hydrogen or aryl.

When *Z* is aryl, preferred *Z* group include phenyl, substituted phenyl, biphenyl, substituted biphenyl and terphenyl groups. Particularly preferred *Z* groups are phenyl, 4-isobutylphenyl, 4'-chlorobiphenyl-4-yl, 4'-trifluoromethylbiphenyl-4-yl, 4-(naphth-2-yl)phenyl, 4-(2-phenylethynyl)phenyl, 4-(3,4-dichlorobenzyloxy)-phenyl, and *p*-terphenyl.

Preferably, *n* is 0 or 1. More preferably, *n* is 1.

Preferably, *x* is 1.

Particularly preferred $-R^a-Y-R^b-(Z)_x$ groups of this invention are selected from the group consisting of:

$-CH_2CH_2-NH-(CH_2)_9CH_3$;

$-CH_2CH_2CH_2-NH-(CH_2)_8CH_3$;

$-CH_2CH_2CH_2CH_2-NH-(CH_2)_7CH_3$;

$-CH_2CH_2-NHSO_2-(CH_2)_9CH_3$;

$-CH_2CH_2-NHSO_2-(CH_2)_{11}CH_3$;

$-CH_2CH_2-S-(CH_2)_8CH_3$;

$-CH_2CH_2-S-(CH_2)_9CH_3$;

$-CH_2CH_2-S-(CH_2)_{10}CH_3$;

$-CH_2CH_2CH_2-S-(CH_2)_8CH_3$;

$-CH_2CH_2CH_2-S-(CH_2)_9CH_3$;

$-CH_2CH_2CH_2-S-(CH_2)_3-CH=CH-(CH_2)_4CH_3$ (*trans*);

$-CH_2CH_2CH_2CH_2-S-(CH_2)_7CH_3$;

$-CH_2CH_2-S(O)-(CH_2)_9CH_3$;

$-CH_2CH_2-S-(CH_2)_6Ph$;

$-CH_2CH_2-S-(CH_2)_8Ph$;

$-CH_2CH_2CH_2-S-(CH_2)_8Ph$;

$-CH_2CH_2-NH-CH_2$-4-(4-Cl-Ph)-Ph;

$-CH_2CH_2-NH-CH_2$-4-[4-$(CH_3)_2CHCH_2$-]-Ph;

$-CH_2CH_2-NH-CH_2$-4-(4-CF_3-Ph)-Ph;

$-CH_2CH_2-S-CH_2$-4-(4-Cl-Ph)-Ph;

$-CH_2CH_2-S(O)-CH_2$-4-(4-Cl-Ph)-Ph;

$-CH_2CH_2CH_2-S-CH_2$-4-(4-Cl-Ph)-Ph;

$-CH_2CH_2CH_2-S(O)-CH_2$-4-(4-Cl-Ph)-Ph;

$-CH_2CH_2CH_2-S-CH_2$-4-[3,4-di-Cl-PhCH_2O-)-Ph;

$-CH_2CH_2-NHSO_2-CH_2$-4-[4-(4-Ph)-Ph]-Ph;

$-CH_2CH_2CH_2-NHSO_2-CH_2$-4-(4-Cl-Ph)-Ph;

$-CH_2CH_2CH_2-NHSO_2-CH_2$-4-(Ph-C≡C-)-Ph;

$-CH_2CH_2CH_2-NHSO_2$-4-(4-Cl-Ph)-Ph; and

$-CH_2CH_2CH_2-NHSO_2$-4-(naphth-2-yl)-Ph.

Other preferred $-R^a-Y-R^b-(Z)_x$ groups are shown in Tables I-IV below.

In yet another of its composition aspects, this invention provides a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a therapeutically effective amount of a compound of formula I or II.

The compounds of this invention are highly effective antibacterial agents. Accordingly, in one of its method aspects, this invention provides a method of treating a mammal having a bacterial disease, the method comprising administering to the mammal a therapeutically effective amount of a compound of formula I or II; or a pharrmaceutical composition comprising a pharmaceutically-acceptable carrier and a therapeutically effective amount of a compound of formula I or II.

In a preferred embodiment, the pharmaceutical compositions of this invention further comprise a cyclodextrin. Preferably, the cyclodextrin is hydroxypropyl-β-cyclodextrin or sulfobutyl ether β-cyclodextrin.

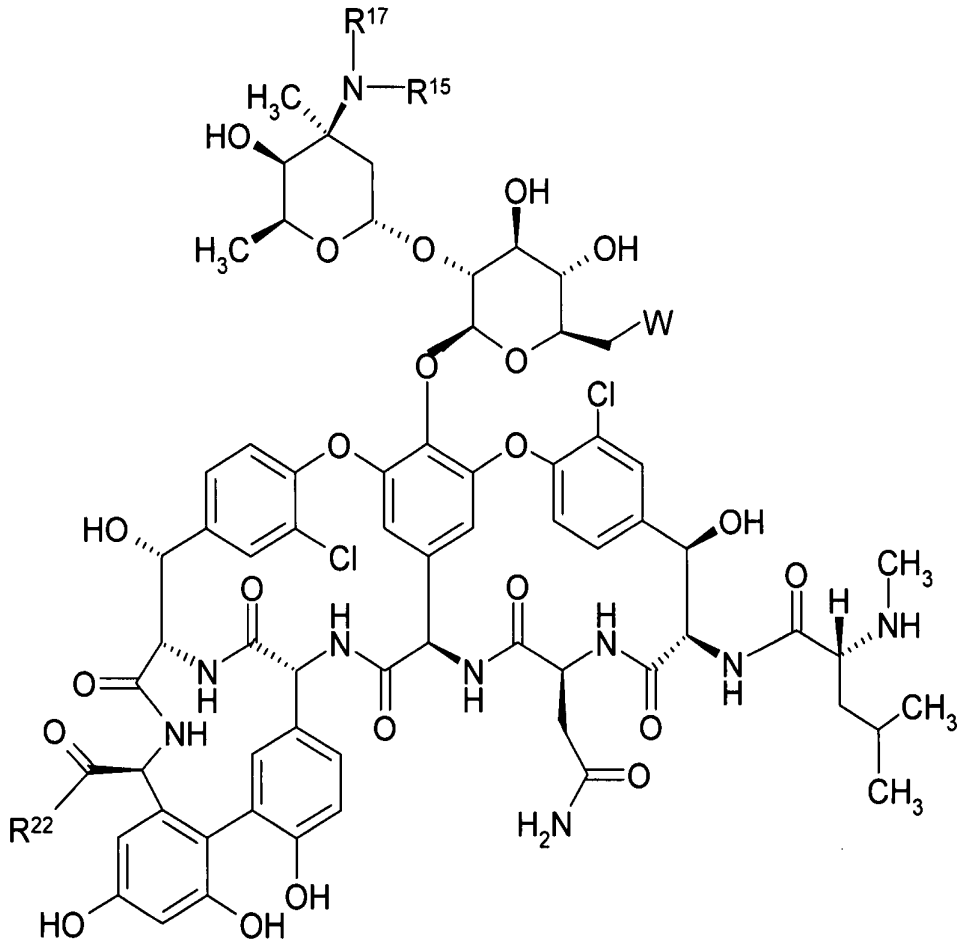
This invention also provides processes and intermediates for preparing glycopeptide derivatives, which processes are described further herein below.

In another of its aspects, this invention is directed to the use of a glycopeptide derivative of formula I or formula II in the manufacture of a formulation or medicament for a medicinal treatment. Preferably, the formulation or medicament is used as an antibacterial agent.

This invention is also directed to intermediates useful for preparing compounds of formula I or II. In one preferred embodiment, this aspect of the invention is directed a compound of formula II, wherein R^{15} is $-R^a-NH-P$, where R^a is as defined herein and *P* is hydrogen or a protecting group; R^{16} and R^{26} are methyl; R^{22} is -OH; R^{23}, R^{24} and R^{27} are hydrogen; R^{25} is isobutyl; *W* is as defined herein; *n* is 1; and salts thereof. In this preferred embodiment, R^a is preferably ethylene ($-CH_2CH_2-$); *P* is hydrogen or 9-fluorenylmethoxycarbonyl (Fmoc); and *W* is amino ($-NH_2$).

Additionally, preferred compounds of this invention are those set forth in the following tables as formulas III, IV, V and VII, and pharmaceutically-acceptable salts thereof:

Table I



III

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
1	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH
2	-CH_2CH_2-N[$(CH_2)_9CH_3$]$_2$	-OH
3	-CH_2CH_2-NH-$(CH_2)_7CH_3$	-OH
4	-CH_2CH_2-NH-$(CH_2)_5CH_3$	-OH
5	-CH_2CH_2-NH-CH_2Ph	-OH
6	-CH_2CH_2-NH-CH_2-4-Ph-Ph	-OH
7	-CH_2CH_2-NH-CH_2-4-(4-Cl-Ph)-Ph	-OH
8	-CH_2CH_2-NH-$(CH_2)_8CH_3$	-OH
9	-CH_2CH_2-NH-CH_2-cyclohexyl	-OH
10	-$CH_2CH_2CH_2$-NH-$(CH_2)_8CH_3$	-OH
11	-$CH_2CH_2CH_2CH_2$-NH-$(CH_2)_7CH_3$	-OH
12	-$CH_2CH_2CH_2CH_2CH_2$-NH-$(CH_2)_6CH_3$	-OH
13	-CH_2CH_2-N(CH_3)-$(CH_2)_9CH_3$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
14	-CH_2CH_2-NH-$(CH_2)_3CH$=$CH(CH_2)_4CH_3$ (*trans*)	-OH
15	-CH_2CH_2-NH-CH_2CH=$C(CH_3)(CH_2)_2$-CH=$C(CH_3)_2$ (*trans, trans*)	-OH
16	-CH_2CH_2-NH-$(CH_2)_8CH(OH)CH_3$	-OH
17	-CH_2CH_2-NH-$(CH_2)_8CH$=CH_2	-OH
18	-CH_2CH_2-NH-CH_2-cyclopropyl	-OH
19	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NH(CH_2)_3N(CH_3)_2$
20	-CH_2CH_2-N[$(CH_2)_9CH_3$]$_2$	-$NH(CH_2)_3N(CH_3)_2$
21	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-*N*-(D-glucosamine)
22	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NHCH(COOH)CH_2COOH$
23	-CH_2CH_2-NH-CH_2-4-(4-Cl-Ph)-Ph	-*N*-(D-glucosamine)
24	-CH_2CH_2-NH-$(CH_2)_8CH_3$	-*N*-(D-glucosamine)
25	-CH_2CH_2-NH-CH_2CH=$C(CH_3)(CH_2)_2$-CH=$C(CH_3)_2$ (*trans, trans*)	-*N*-(D-glucosamine)
26	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NHCH(CO_2CH_3)CH_2CO_2CH_3$

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
27	-CH_2CH_2-NH-$(CH_2)_8CH(OH)CH_3$	-NHCH(COOH)CH_2COOH
28	-CH_2CH_2-NHC(O)-$(CH_2)_6CH(CH_3)CH_3$	-OH
29	-CH_2CH_2-NHC(O)-$(CH_2)_8CH_3$	-OH
30	-CH_2CH_2-OC(O)-$(CH_2)_8CH_3$	-OH
31	-CH_2-C(O)O-$(CH_2)_9CH_3$	-OH
32	-CH_2-C(O)NH-$(CH_2)_9CH_3$	-OH
33	-CH_2-C(O)O-$(CH_2)_7CH_3$	-OH
34	-CH_2CH_2-$NHSO_2$-$(CH_2)_7CH_3$	-OH
35	-CH_2CH_2-OSO_2-$(CH_2)_7CH_3$	-OH
36	-CH_2CH_2-S-$(CH_2)_9CH_3$	-OH
37	-CH_2CH_2-NHC(O)-$(CH_2)_6CH_3$	-OH
38	-CH_2CH_2-NHC(O)-$(CH_2)_7CH_3$	-OH
39	-CH_2CH_2-NHC(O)-$(CH_2)_9CH_3$	-OH
40	-CH_2-C(O)NH-$(CH_2)_6CH_3$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
41	-CH_2-C(O)NH-$(CH_2)_7CH_3$	-OH
42	-CH_2-C(O)NH-$(CH_2)_8CH_3$	-OH
43	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NH$(CH_2)_3$-morpholin-4-yl
44	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NH$(CH_2)_3$-NH-$(CH_2)_2CH_3$
45	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NH$(CH_2)_2$-piperidin-1-yl
46	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NH$(CH_2)_4$NHC(N)NH_2
47	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NH$(CH_2)_2$-$N^+(CH_3)_3$
48	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NHCH(COOH)$(CH_2)_3$NHC(N)NH_2
49	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NH[$(CH_2)_3$NH-]$_3$H
50	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-N[$(CH_2)_3N(CH_3)_2]_2$
51	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NH$(CH_2)_3$-imidiazol-1-yl
52	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NHCH_2$-4-pyridyl
53	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NH$(CH_2)_3CH_3$
54	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NH$(CH_2)_2$OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
55	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NH(CH_2)_5OH$
56	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NH(CH_2)_2OCH_3$
57	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NHCH_2$-tetrahydrofuran-2-yl
58	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$N[(CH_2)_2OH]_2$
59	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NH(CH_2)_2N[(CH_2)_2OH]_2$
60	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-*N*-(glucamine)
61	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NHCH_2COOH$
62	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NHCH(COOH)CH_2OH$
63	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NH(CH_2)_2COOH$
64	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NH(CH_2)_3SO_3H$
65	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NHCH(COOH)(CH_2)_3COOH$
66	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NHCH(COOH)(CH_2)_2NH_2$
67	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NHCH(COOH)(CH_2)_3NH_2$
68	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NHCH(COOH)CH_2CO_2(CH_2)_3$-$N^+(CH_3)_3$

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
69	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NHCH(COOH)CH_2CO_2-$(CH_2)_2$C(O)N$(CH_3)_2$
70	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NHCH(COOH)CH_2CO_2-$(CH_2)_3$-morpholin-4-yl
71	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NHCH(COOH)$CH_2CO_2(CH_2)_2OC(O)C(CH_3)_3$
72	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NHCH(CH_2COOH)$CO_2(CH_2)_3$-$N^+(CH_3)_3$
73	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NHCH(CH_2COOH)$CO_2(CH_2)_2$C(O)N$(CH_3)_2$
74	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NHCH(CH_2COOH)$CO_2(CH_2)_3$-morpholin-4-yl
75	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NHCH(CH_2COOH)$CO_2(CH_2)_2OC(O)C(CH_3)_3$
76	-CH_2CH_2-NH-$(CH_2)_6$Ph	-OH
77	-CH_2CH_2-NH-$(CH_2)_8$Ph	-OH
78	-CH_2CH_2-NH-CH_2Ph	-OH
79	-CH_2CH_2-NH-CH_2-4-Cl-Ph	-OH
80	-CH_2CH_2-NH-CH_2-4-[$CH_3(CH_2)_2O$-]Ph	-OH
81	-CH_2CH_2-NH-CH_2-4-[$CH_3(CH_2)_4O$-]Ph	-OH
82	-CH_2CH_2-NH-CH_2-4-[$CH_3(CH_2)_6O$-]Ph	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
83	-CH_2CH_2-NH-CH_2-4-[$CH_3(CH_2)_8O$-]Ph	-OH
84	-CH_2CH_2-NH-CH_2-4-[$CH_3(CH_2)_2$-]Ph	-OH
85	-CH_2CH_2-NH-CH_2-4-[$CH_3(CH_2)_3$-]Ph	-OH
86	-CH_2CH_2-NH-CH_2-4-[$CH_3(CH_2)_4$-]Ph	-OH
87	-CH_2CH_2-NH-CH_2-4-(PhO-)Ph	-OH
88	-CH_2CH_2-NH-CH_2-4-(PhS-)Ph	-OH
89	-CH_2CH_2-NH-CH_2-3-(PhO-)Ph	-OH
90	-CH_2CH_2-NH-CH_2-4-(cyclohexyl-)Ph	-OH
91	-CH_2CH_2-NH-CH_2-4-{4-[$CH_3(CH_2)_4O$-]-Ph}-Ph	-OH
92	-CH_2CH_2-NH-CH_2-4-CF_3-Ph	-OH
93	-CH_2CH_2-NH-CH_2-4-($PhCH_2O$-)Ph	-OH
94	-CH_2CH_2-NH-CH_2-4-(4-CH_3-$PhCH_2O$-)Ph	-OH
95	-CH_2CH_2-NH-$(CH_2)_7CH(CH_3)_2$	-OH
96	-$(CH_2)_5$-NH-$(CH_2)_6CH_3$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
97	-$(CH_2)_3$-NH-$(CH_2)_9CH_3$	-OH
98	-$(CH_2)_4$-NH-$(CH_2)_9CH_3$	-OH
99	-$(CH_2)_5$-NH-$(CH_2)_9CH_3$	-OH
100	-CH_2CH_2-NH-$(CH_2)_7CH_3$	-OH
101	-CH_2CH_2-NH-CH_2-cyclohexyl	-OH
102	-CH_2CH_2-S-$(CH_2)_7CH_3$	-OH
103	-CH_2CH_2-OC(O)-$(CH_2)_6CH_3$	-OH
104	-CH_2CH_2-$NHSO_2$-$(CH_2)_9CH_3$	-OH
105	-CH_2CH_2-OSO_2-$(CH_2)_9CH_3$	-OH
106	-CH_2CH_2-NH-CH_2CH=CH-CH=CH$(CH_2)_4CH_3$ (*trans, trans*)	-OH
107	-CH_2CH_2-NH-CH_2CH=CH-CH=CH$(CH_2)_3CH_3$ (*trans, trans*)	-OH
108	-CH_2CH_2-NH-CH_2CH=CH-CH=CHCH_2CH_3 (*trans, trans*)	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
109	-CH_2CH_2-NH-CH_2CH=CH-CH_2CH_2CH=CHCH_2CH_3 (*trans, trans*)	-OH
110	-CH_2CH_2-NH-CH_2-4-Cl-Ph	-OH
111	-CH_2CH_2-NH-CH_2-4-(PhCH_2O-)Ph	-OH
112	-CH_2CH_2-NH-CH_2-4-(4-CH_3-PhCH_2O-)Ph	-OH
113	-CH_2CH_2-NH-CH_2-4-(4-Cl-PhCH_2O-)Ph	-OH
114	-CH_2CH_2-NH-CH_2-4-[$CH_3(CH_2)_2$O-]Ph	-OH
115	-CH_2CH_2-NH-CH_2-4-[$CH_3(CH_2)_4$O-]Ph	-OH
116	-CH_2CH_2-NH-CH_2-4-[$CH_3(CH_2)_6$O-]Ph	-OH
117	-CH_2CH_2-NH-CH_2-4-[$CH_3(CH_2)_8$O-]Ph	-OH
118	-CH_2CH_2-NH-CH_2-4-[$(CH_3)_2CHCH_2$-]Ph	-OH
119	-CH_2CH_2-NH-CH_2-4-(Ph-S-)Ph	-OH
120	-CH_2CH_2-NH-CH_2-4-(4-CF_3-Ph)-Ph	-OH
121	-CH_2CH_2-NH-CH_2-4-{4-[$CH_3(CH_2)_4$O-]-Ph}-Ph	-OH
122	-CH_2CH_2-NH-$(CH_2)_6$Ph	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
123	-CH_2CH_2-NH-$(CH_2)_8$Ph	-OH
124	-CH_2CH_2-NH-$(CH_2)_9CH_3$ R^{17} = -CH_2COOH	-OH
125	-CH_2CH_2-NH-$(CH_2)_9CH_3$ R^{17} = -$CH_2[CH(OH)]_4COOH$	-OH
126	-CH_2CH_2-NH-$(CH_2)_9CH_3$ R^{17} = -CH_2-(imidazol-4-yl)	-OH
127	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NH(CH_2)_3CH_3$
128	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NHCH(COOH)CH_2OH
129	-CH_2CH_2-NH-CH_2CH_2-(cyclopropyl)	-OH
130	-CH_2-C(O)O-$(CH_2)_7CH_3$	-OH
131	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NHCH(COOH)$CH_2CO_2CH_3$
132	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NHCH(CH_2COOH)$CO_2(CH_2)_2N(CH_3)_2$
133	-CH_2CH_2-NH-CH_2CH=CH-CH=$CHCH_3$ (*trans, trans*)	-OH
134	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NHCH(COOH)$CH_2CO_2CH_2$C(O)N$(CH_3)_2$
135	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NHCH(CH_2COOH)CO_2CH_2C(O)N$(CH_3)_2$
136	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NHCH(CH_2COOH)CO_2CH_3

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
137	-CH_2CH_2-NHC(O)-CH_2CH_2-C(O)NH$CH_2CH_2NH_2$	-NH$CH_2CH_2CH_2N(CH_3)_2$
138	-CH_2CH_2-$NHSO_2$-4-Ph-Ph	-OH
139	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NH$CH_2CH_2CO_2CH_3$
140	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NHCH[$CH_2CO_2CH_2C(O)N(CH_3)_2$]$CO_2CH_2$-C(O)-$N(CH_3)_2$
141	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NH$CH_2CO_2CH_3$
142	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-*N*-(methyl 3-amino-3-deoxyamnnopyranoside)
143	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-*N*-(methyl 3-amino-2,3-6-trideoxyhexopyranoside)
144	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-*N*-[2-amino-2-deoxy-6-(dihydrogen phosphate)glucopyranose
145	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-*N*-(2-amino-2-deoxygluconic acid)
146	-CH_2CH_2-N(C(O)CH_2NHCH_3)-$(CH_2)_9CH_3$	-OH
147	-CH_2CH_2-N(C(O)CH_3)-$(CH_2)_9CH_3$	-OH
148	-CH_2CH_2-S(O)-$(CH_2)_9CH_3$	-OH
149	-CH_2CH_2-NH-$(CD_2)_9CD_3$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
150	-CH_2CH_2-N(CH_2COOH)-$(CH_2)_9CH_3$	-OH
151	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NH(CH_2)_4COOH$
152	-CH_2CH_2-$NHSO_2$-4-(4-Cl-Ph)-Ph	-OH
153	-CH_2CH_2-N($CH_2CO_2CH_3$)-$(CH_2)_9CH_3$	-OH
154	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-*N*-(*N*-CH_3-D-glucamine)
155	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NH(CH_2)_6COOH$
156	-CH_2-C(O)O-CH_2CH_3	-OH
157	-CH_2CH_2-S(O)-$(CH_2)_7CH_3$	-OH
158	-CH_2CH_2-$NHSO_2$-3-(4-Cl-Ph)-Ph	-OH
159	-CH_2CH_2-$NHSO_2$-$(CH_2)_7CH_3$	-OH
160	-$CH_2CH_2CH_2$-$NHSO_2$-4-(4-Cl-Ph)-Ph	-OH
161	-CH_2CH_2-NH-CH_2-4-(4-Cl-$PhCH_2O$-)-Ph	-*N*-(D-glucosamine)
162	-CH_2CH_2-NH-CH_2-4-(4-Cl-$PhCH_2O$-)-Ph	-$NHCH(COOH)CH_2COOH$
163	-CH_2CH_2-$NHSO_2$-4-(naphth-2-yl)-Ph	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
164	-CH_2CH_2-NH-$(CH_2)_{11}CH_3$	-OH
165	-CH_2CH_2-N[C(O)CH(NH_2)$(CH_2)_4NH_2$]-$(CH_2)_9CH_3$ (R isomer)	-OH
166	-CH_2CH_2-$NHSO_2$-$(CH_2)_9CH_3$	-*O*-(D-glucose)
167	-CH_2CH_2-$NHSO_2$-$(CH_2)_9CH_3$	-N[$(CH_2)_2OH]_2$
168	-$CH_2CH_2CH_2$-NH-CH_2-4-(4-CF_3-Ph)-Ph	-*O*-(D-glucose)
169	-$CH_2CH_2CH_2$-NH-CH_2-4-(4-CF_3-Ph)-Ph	-N[$(CH_2)_2OH]_2$
170	-$CH_2CH_2CH_2$-NH-CH_2-4-(4-CF_3-Ph)-Ph	-OH
171	-$CH_2CH_2CH_2$-NH-CH_2-4-(4-CH_3O-Ph)-Ph	-OH
172	-CH_2CH_2-NH-CH_2-4-[$(CH_3)_3CO$]-Ph	-OH
173	-CH_2CH_2-NH-CH_2-3,4-di-(CH_3CH_2O)-Ph	-OH
174	-CH_2CH_2-NH-CH_2-4-[$(CH_3)_2CH$]-Ph	-OH
175	-CH_2CH_2-NH-CH_2-4-[$CH_3(CH_2)_3C{\equiv}C$]-Ph	-OH
176	-CH_2CH_2-NH-CH_2-4-[$(CH_3)_2CHO$]-Ph	-OH
177	-CH_2CH_2-NH-CH_2-4-(Ph$C{\equiv}C$)-Ph	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
178	-CH_2CH_2-NH-CH_2-4-[$(CH_3)_3C$]-Ph	-OH
179	-CH_2CH_2-NH-CH_2-5-(PhC≡C)-thiophen-2-yl	-OH
180	-CH_2CH_2-NH-CH_2-4-(PhCH=CH-)Ph (*trans*)	-OH
181	-CH_2CH_2-NH-CH_2-$(CH=CH)_4$-CH_3 (*trans, trans, trans, trans*)	-OH
182	-CH_2CH_2-N(C(O)Ph)-$(CH_2)_9CH_3$	-OH
183	-CH_2CH_2-NH-CH_2-4-[4-$(CH_3)_3$C-thiazol-2-yl]-Ph	-OH
184	-CH_2CH_2-N[$(CH_2)_9CH_3$]-C(O)CH_2-S-4-pyridyl	-OH
185	-CH_2CH_2-N[$(CH_2)_9CH_3$]-C(O)-2-[PhCH(CH_3)NHC(O)-]Ph (R isomer)	-OH
186	-CH_2CH_2-N[$(CH_2)_9CH_3$]-C(O)-(1-$PhCH_2OC$(O)-2-oxoimidazolidin-5-yl) (S isomer)	-OH
187	-CH_2CH_2-N[$(CH_2)_9CH_3$]-C(O)-1-HO-cyclopropyl	-OH
188	-CH_2CH_2-N(C(O)CH_2-naphth-2-yl)-$(CH_2)_9CH_3$	-OH
189	-CH_2CH_2-N[C(O)$(CH_2)_9CH_2OH$]-$(CH_2)_9CH_3$	-OH
190	-CH_2CH_2-N[C(O)$CH_2(OCH_2CH_2)_2OCH_3$]-$(CH_2)_9CH_3$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
191	-CH_2CH_2-N[C(O)CH_2CH(Ph)$_2$]-$(CH_2)_9CH_3$	-OH
192	-CH_2CH_2-N(C(O)CH_2-3-HO-Ph)-$(CH_2)_9CH_3$	-OH
193	-CH_2CH_2-N(C(O)CH_2-NHC(O)-3-CH_3-Ph)-$(CH_2)_9CH_3$	-OH
194	-CH_2CH_2-N(C(O)CH_2CH_2-O-Ph)-$(CH_2)_9CH_3$	-OH
195	-CH_2CH_2-N(C(O)CH_2CH_2-3-pyridyl)-$(CH_2)_9CH_3$	-OH
196	-CH_2CH_2-N(C(O)$(CH_2)_3$-4-CH_3O-Ph)-$(CH_2)_9CH_3$	-OH
197	-CH_2CH_2-N(C(O)-indol-2-yl)-$(CH_2)_9CH_3$	-OH
198	-CH_2CH_2-N{C(O)-1-[CH_3COC(O)-]-pyrrolidin-2-yl}-$(CH_2)_9CH_3$	-OH
199	-CH_2CH_2-N(C(O)CH_2-NHC(O)-CH=CH-furan-2-yl)-$(CH_2)_9CH_3$ (*trans*)	-OH
200	-CH_2CH_2-N[C(O)-1-CH_3CH_2-7-CH_3-4-oxo-1,4-dihydro[1,8]naphthyridin-3-yl]-$(CH_2)_9CH_3$	-OH
201	-CH_2CH_2-N(C(O)-1,3-benzodioxol-5-yl)-$(CH_2)_9CH_3$	-OH
202	-CH_2CH_2-N(C(O)CH_2-4-oxo-2-thiooxothiazolidin-3-yl)-$(CH_2)_9CH_3$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
203	-CH_2CH_2-N(C(O)-3,4,5-tri-HO-cyclohex-1-en-1-yl)-$(CH_2)_9CH_3$ (R,S,R isomer)	-OH
204	-CH_2CH_2-N(C(O)$CH_2CH_2C(O)NH_2$)-$(CH_2)_9CH_3$	-OH
205	-CH_2CH_2-N(C(O)CH_2-5-CH_3-2,4-dioxo-3,4-dihydropyrimidin-1-yl)-$(CH_2)_9CH_3$	-OH
206	-CH_2CH_2-N(C(O)CH=CH-imidazol-4-yl)-$(CH_2)_9CH_3$ (*trans*)	-OH
207	-CH_2CH_2-N[C(O)CH($CH_2CH_2C(O)NH_2$)-NHC(O)O-CH_2Ph]-$(CH_2)_9CH_3$ (S isomer)	-OH
208	-CH_2CH_2-N[C(O)CH(CH_2OH)NHC(O)O-CH_2Ph]-$(CH_2)_9CH_3$ (S isomer)	-OH
209	-CH_2CH_2-N[C(O)CH[CH(OH)CH_3]NH-C(O)O-CH_2Ph]-$(CH_2)_9CH_3$ (S isomer)	-OH
200	-CH_2CH_2-N(C(O)CH_2NHSO_2-4-CH_3-Ph)-$(CH_2)_9CH_3$	-OH
211	-CH_2CH_2-N(C(O)$(CH_2)_3$-NH_2)-$(CH_2)_9CH_3$	-OH
212	-CH_2CH_2-N(C(O)-pyrrolidin-2-yl)-$(CH_2)_9CH_3$ (R isomer)	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
213	-CH_2CH_2-N(C(O)-pyrrolidin-2-yl)-$(CH_2)_9CH_3$ (S isomer)	-OH
214	-CH_2CH_2-N(C(O)CH(NH_2)$(CH_2)_4$-NH_2)-$(CH_2)_9CH_3$ (S isomer)	-OH
215	-CH_2CH_2-N(C(O)CH(NH_2)CH_2-3-HO-Ph)-$(CH_2)_9CH_3$	-OH
216	-CH_2CH_2-N(C(O)CH(NH_2)CH_3)-$(CH_2)_9CH_3$ (R isomer)	-OH
217	-CH_2CH_2-N[C(O)CH(CH_2OH)NHC(O)-CH_3]-$(CH_2)_9CH_3$ (S isomer)	-OH
218	-CH_2CH_2-N[C(O)CH(NHC(O)CH_3)-$(CH_2)_3$-NHC(NH)NH_2]-$(CH_2)_9CH_3$ (S isomer)	-OH
219	-CH_2CH_2-N(C(O)CH_2NHC(O)CH_3)-$(CH_2)_9CH_3$	-OH
220	-CH_2CH_2-N(C(O)CH(CH_3)OC(O)CH-(NH_2)CH_3)-$(CH_2)_9CH_3$ (R,R isomer)	-OH
221	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-NH$(CH_2)_3$OC(O)CH(NH_2)CH_3
222	-CH_2CH_2-N(C(O)-5-oxopyrrolidin-2-yl)-$(CH_2)_9CH_3$ (R isomer)	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
223	-CH_2CH_2-NHC(O)-$CH_2CH(CH_2CH_2Ph)$-{3-[4-(9H-fluroen-9-yl$CH_2OC(O)NH(CH_2)_4$-]-1,4-dioxohexahydro-1,2-α-pyrazin-2-yl} (S,S,S isomer)	-OH
224	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-$NH(CH_2)_4CH$(C(O)-2-HOOC-pyrrolidin-1-yl)NHCH(COOH)-CH_2CH_2Ph (S,S isomer)
225	-CH_2CH_2-$NHSO_2$-4-(2-Cl-Ph)-Ph	-OH
226	-CH_2CH_2-$NHSO_2$-4-[4-$(CH_3)_3$C-Ph]-Ph	-OH
227	-CH_2CH_2-$NHSO_2$-4-[4-(Ph)-Ph-]Ph	-OH
228	-CH_2CH_2-NH-4-(4-CF_3-Ph)-Ph	-OH
229	-CH_2CH_2-S-$(CH_2)_8$Ph	-OH
230	-CH_2CH_2-S-$(CH_2)_3CH$=$CH(CH_2)_4CH_3$ (*trans*)	-OH
231	-CH_2CH_2-S-$CH_2CH_2(CF_2)_5CF_3$	-OH
232	-CH_2CH_2-S-CH_2-4-[$(CH_3)_2CHCH_2$-]Ph	-OH
233	-CH_2CH_2-S-$(CH_2)_{11}CH_3$	-OH
234	-CH_2CH_2-S-$(CH_2)_8CH_3$	-OH

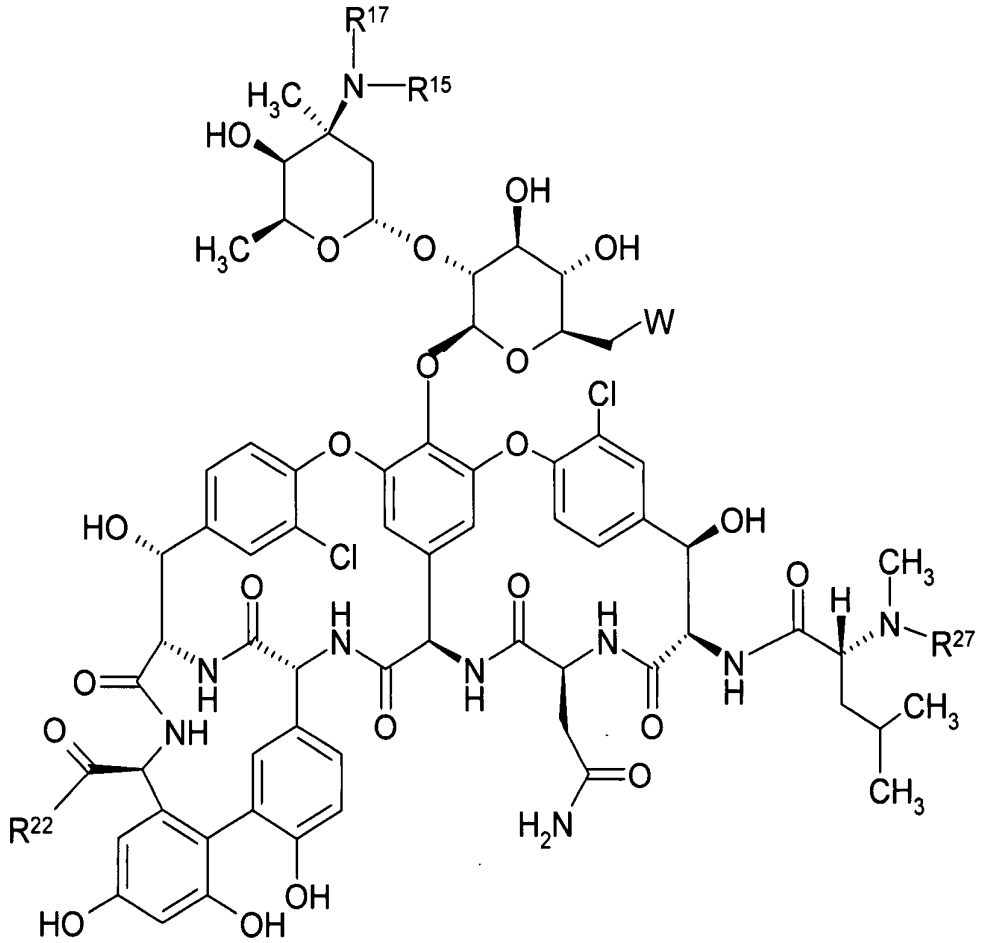
No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
235	-CH_2CH_2-S-CH_2-3,4-di-(PhCH_2O-)Ph	-OH
236	-$CH_2CH_2CH_2$-S-$(CH_2)_8$Ph	-OH
237	-$CH_2CH_2CH_2$-S-$(CH_2)_8CH_3$	-OH
238	-$CH_2CH_2CH_2$-S-$(CH_2)_9CH_3$	-OH
239	-$CH_2CH_2CH_2$-S-$(CH_2)_6$Ph	-OH
240	-$CH_2CH_2CH_2CH_2$-S-$(CH_2)_7CH_3$	-OH
241	-CH_2CH_2-S-$(CH_2)_6$Ph	-OH
242	-CH_2CH_2-S-$(CH_2)_{10}$Ph	-OH
243	-$CH_2CH_2CH_2$-S-CH_2-4-[$(CH_3)_2CHCH_2$-]Ph	-OH
244	-CH_2CH_2-S-$(CH_2)_3CH$=$CH(CH_2)_4CH_3$ (*trans*)	-OH
245	-CH_2CH_2-S-CH_2-4-[3,4-di-Cl-PhCH_2O-]Ph	-OH
246	-$CH_2CH_2CH_2$-S-CH_2-4-[3,4-di-Cl-PhCH_2O-]Ph	-OH
247	-CH_2CH_2-SO-4-(4-Cl-Ph)-Ph	-OH
248	-$CH_2CH_2CH_2$-SO-4-(4-Cl-Ph)-Ph	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
249	-CH_2CH_2-S-$(CH_2)_{10}CH_3$	-OH
250	-$CH_2CH_2CH_2$-S-$(CH_2)_{10}CH_3$	-OH
251	-$CH_2CH_2CH_2$-S-CH_2-4-[$CH_3(CH_2)_4O$-]Ph	-OH
252	-$CH_2CH_2CH_2$-S-CH_2CH=CH-CH=$CH(CH_2)_4CH_3$ (*trans, trans*)	-OH
253	-CH_2CH_2-S-CH_2-4-[4-Cl-PhCH_2O-]Ph	-OH
254	-$CH_2CH_2CH_2$-S-CH_2-4-[4-Cl-PhCH_2O-]Ph	-OH
255	-CH_2CH_2-NH-$(CH_2)_9CH_3$	tetrazol-5-yl
256	-CH_2CH_2-S-$(CH_2)_9CH_3$	-*N*-(D-glucosamine)
257	-$CH_2CH_2CH_2$-S-CH_2-4-(4-CF_3-Ph-)Ph	-OH
258	-CH_2CH_2-S-$(CH_2)_9CH_3$	tetrazol-5-yl
259	-$CH_2CH_2CH_2$-S-CH_2-4-(4-F-PhSO_2NH-)Ph	-OH
260	-$CH_2CH_2CH_2$-S-$(CH_2)_8CH_3$	-OH
261	-$CH_2CH_2CH_2$-S(O)-$(CH_2)_6$Ph	-OH
262	-CH_2CH_2-S(O)-$(CH_2)_8$Ph	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}
263	-CH_2CH_2-S-$(CH_2)_3$-4-Cl-Ph	-OH
264	-CH_2CH_2-S-$(CH_2)_6$-4-Cl-Ph	-OH
265	-CH_2CH_2-SO_2-$(CH_2)_9CH_3$	-OH
406	-H	-NH-CH_2CH_2-NH-$(CH_2)_9CH_3$

Ph = phenyl

Table II



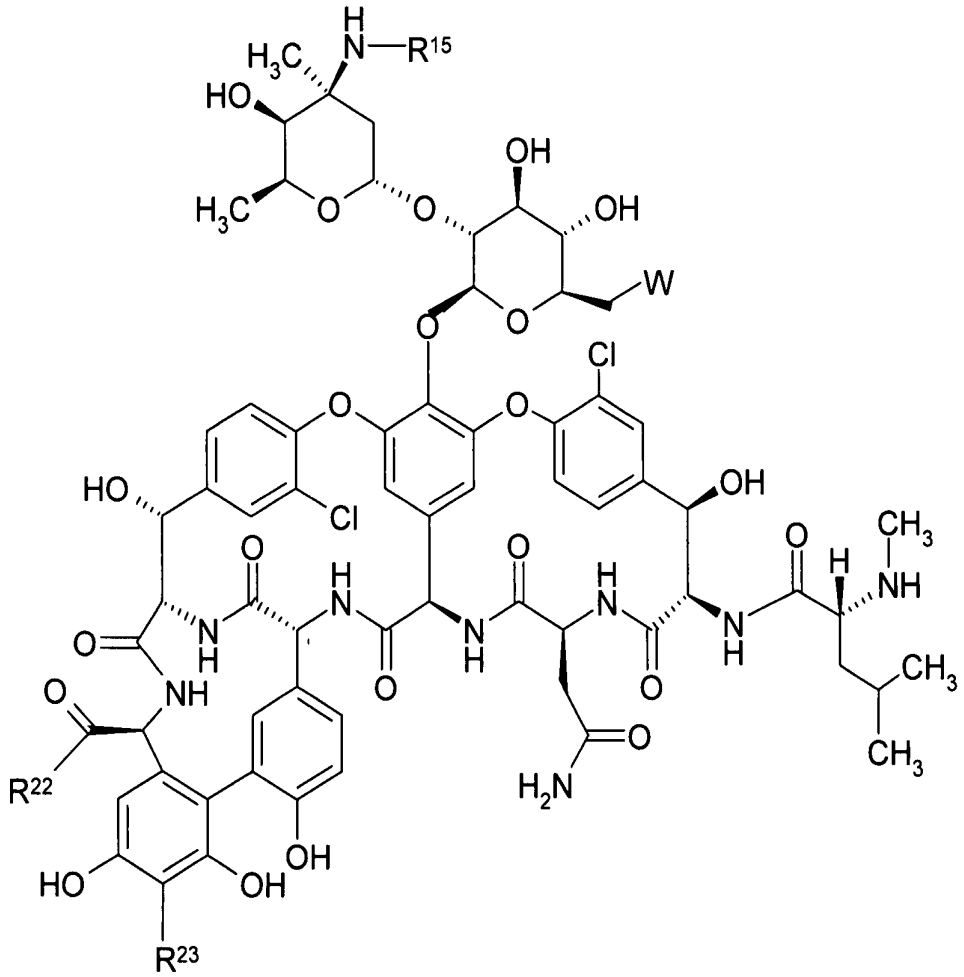
IV

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}	R^{27}
266	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-CH_2-[CH(OH)]$_5CH_2OH$
267	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-$CH_2CH(OH)CH_2OH$
268	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-$CH_2CH_2NH_2$
269	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-$CH_2C(O)OCH_2CH_3$
270	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-CH_2COOH
271	-CH_2CH_2-NH-$(CH_2)_9CH_3$ R^{17} = -CH_2COOH	-OH	-CH_2COOH
272	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-CH_2-2-pyridyl
273	-CH_2CH_2-NH-$(CH_2)_8CH_3$	-OH	-CH_2[CH(OH)]$_4$COOH
274	-H	-$NHCH_2C(O)CH_2C(O)N(CH_3)_2$	-H
275	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-CH_2-3-HOOC-Ph
276	-CH_2CH_2-N(C(O)CH(NH_2)-$(CH_2)_4NH_2$)-$(CH_2)_9CH_3$ (R isomer)	-OH	-C(O)CH(NH_2)$(CH_2)_4NH_2$ (R isomer)
277	-CH_2CH_2-NH-$(CH_2)_{11}CH_3$	-OH	-CH_2COOH

No.	R^{15} (R^{17} = H, unless otherwise indicated; W = -NH_2)	R^{22}	R^{27}
278	-CH_2CH_2-N(C(O)Ph)-$(CH_2)_9CH_3$	-OH	-C(O)Ph
279	-CH_2CH_2-N(C(O)CH_2NHC(O)CH_3)-$(CH_2)_9CH_3$	-OH	-C(O)CH_2NHC(O)CH_3
280	-CH_2CH_2-S-$(CH_2)_3$CH=CH$(CH_2)_4CH_3$ (*trans*)	-OH	-CH_2CH_2-S-$(CH_2)_3$CH=CH$(CH_2)_4CH_3$ (*trans*)
281	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH_3

Ph = phenyl

Table III



V

No.	R^{15} (W = -NH_2)	R^{22}	R^{23}
282	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)
283	-CH_2CH_2-NH-CH_2-4-(4-Cl-Ph)Ph	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)
284	-CH_2CH_2-NH-$(CH_2)_8CH(OH)CH_3$	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)
285	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-N-(-D-glucosamine)	-CH_2-*N*-(*N*-CH_3-D-glucamine)
286	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)
287	-H	-OH	-CH_2-NH-CH_2CH_2-NH-$(CH_2)_9CH_3$
288	-CH_2CH_2-NH-CH_2-4-(4-Cl-Ph)Ph	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)
289	-H	-NH-$(CH_2)_3$-$N(CH_3)_2$	-CH_2-NH-CH_2CH_2-NHC(O)-$(CH_2)_3COOH$
290	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-CH_2-NH-$(CH_2)_9CH_3$
291	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-CH_2-NH-CH_2CH_2-COOH
292	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-CH_2-NH-$(CH_2)_5$-COOH
293	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-CH_2-(morpholin-4-yl)
294	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-CH_2-NH-CH_2CH_2-O-CH_2CH_2OH
295	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-CH_2-NH-$CH_2CH(OH)CH_2OH$

No.	R^{15} (W = $-NH_2$)	R^{22}	R^{23}
296	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-N[CH_2CH_2OH]_2$
297	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NH-(CH_2)_3-N(CH_3)_2$
298	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-N[(CH_2)_3-N(CH_3)_2]_2$
299	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NH-(CH_2)_3$-(imidazol-1-yl)
300	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NH-(CH_2)_3$-(morpholin-4-yl)
301	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NH-(CH_2)_4-NHC(NH)NH_2$
302	$-CH_2CH_2-NHSO_2-(CH_2)_7CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
303	$-CH_2CH_2-NHSO_2-(CH_2)_9CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
304	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(COOH)CH_2COOH$	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
305	$-CH_2CH_2-NH-(CH_2)_7CH(OH)CH_2CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
306	$-CH_2CH_2-NH-(CH_2)_{10}OH$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
307	$-CH_2CH_2-NHSO_2$-4-Ph-Ph	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
308	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
309	$-CH_2CH_2-NH-(CH_2)_7CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)

No.	R^{15} (W = -NH_2)	R^{22}	R^{23}
310	-CH_2CH_2-NH-$(CD_2)_9CD_3$	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)
311	-CH_2CH_2-S-$(CH_2)_9CH_3$	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)
312	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-CH_2-*N*-(2-amino-2-deoxygluconic acid)
313	-H	-OH	-CH_2-NH-CH_2CH_2-NH-$(CH_2)_7CH_3$
314	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-CH_2-NHCH(COOH)CH_2COOH
315	-H	-OH	-CH_2-NH-CH_2CH_2-$NHSO_2$-$(CH_2)_7CH_3$
316	-H	-OH	-CH_2-NH-CH_2CH_2-$NHSO_2$-$(CH_2)_9CH_3$
317	-H	-OH	-CH_2-NH-CH_2CH_2-$NHSO_2$-$(CH_2)_{11}CH_3$
318	-H	-OH	-CH_2-NH-CH_2CH_2-NH-$(CH_2)_7CH_3$
319	-CH_2CH_2-SO-$(CH_2)_9CH_3$	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)
320	-CH_2CH_2-$NHSO_2$-CH_2-4-(4-Cl-Ph)Ph	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)
321	-CH_2CH_2-NH-CH_2CH=CH-CH=CH$(CH_2)_4CH_3$ (*trans, trans*)	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)
322	-CH_2CH_2-$NHSO_2$-$(CH_2)_9CH_3$	-OH	-CH_2-NH-CH_2CH_2-O-CH_2CH_2OH
323	-$CH_2CH_2CH_2$-$NHSO_2$-CH_2-4-(4-Cl-Ph)Ph	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)

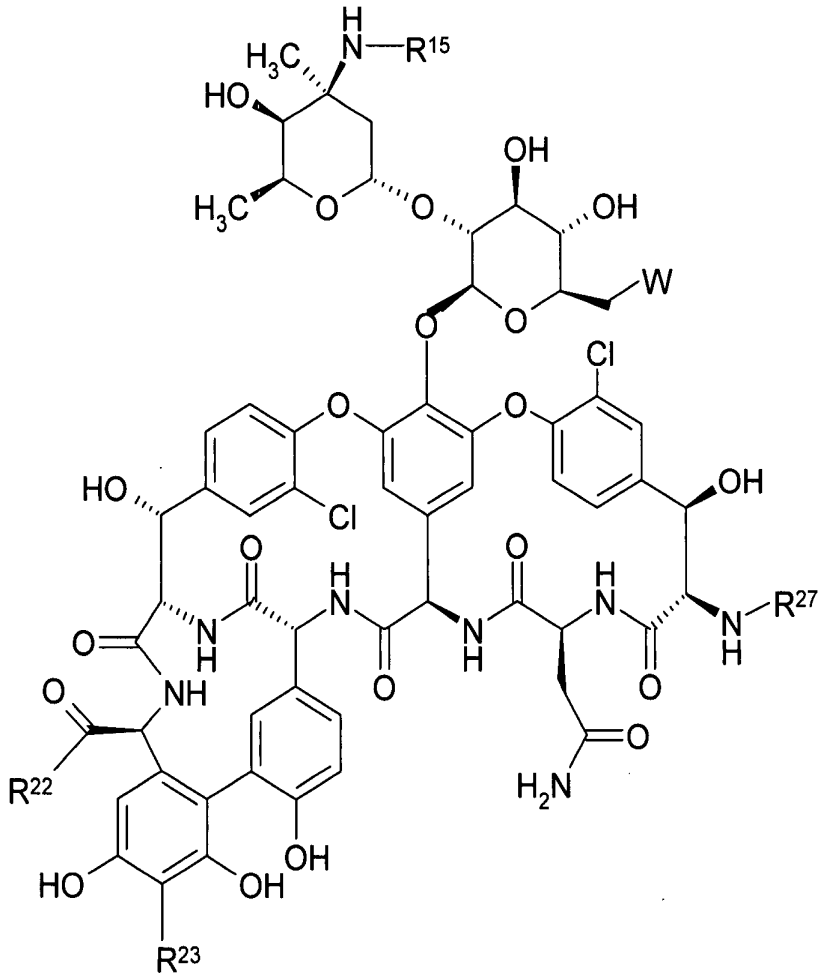
No.	R[15] (W = -NH$_2$)	R[22]	R[23]
324	-CH$_2$CH$_2$-NH-CH$_2$-4-[(CH$_3$)$_2$CHCH$_2$-]Ph	-OH	-CH$_2$-*N*-(*N*-CH$_3$-D-glucamine)
325	-CH$_2$CH$_2$-NH-CH$_2$-4-[(CH$_3$)$_2$CHCH$_2$-]Ph	-OH	-CH$_2$-NH-CH$_2$CH$_2$-O-CH$_2$CH$_2$OH
326	-CH$_2$CH$_2$-NH-CH$_2$-4-[4-Cl-PhCH$_2$O-]Ph	-OH	-CH$_2$-*N*-(*N*-CH$_3$-D-glucamine)
327	-CH$_2$CH$_2$-NH-(CH$_2$)$_9$CH$_3$	-OH	-CH$_2$-NHCH$_2$CH$_2$C(O)-*N*-(D-glucosamine)
328	-CH$_2$CH$_2$-NH-(CH$_2$)$_9$CH$_3$	-OH	-CH$_2$-NH-CH$_2$CH$_2$-O-CH$_2$CH$_2$OH
329	-CH$_2$CH$_2$-NH-(CH$_2$)$_9$CH$_3$	-NHCH(COOH)CH$_2$COOH	-CH$_2$-NH-CH$_2$CH$_2$-O-CH$_2$CH$_2$OH
330	-CH$_2$CH$_2$-NH-(CH$_2$)$_{11}$CH$_3$	-OH	-CH$_2$-*N*-(*N*-CH$_3$-D-glucamine)
331	-CH$_2$CH$_2$CH$_2$-NH-CH$_2$-4-(4-CF$_3$-Ph)Ph	-OH	-CH$_2$-NH-CH$_2$CH$_2$-O-CH$_2$CH$_2$OH
332	-CH$_2$CH$_2$CH$_2$-NH-CH$_2$-4-(4-CF$_3$-Ph)Ph	-OH	-CH$_2$-*N*-(*N*-CH$_3$-D-glucamine)
333	-CH$_2$CH$_2$CH$_2$-NH-CH$_2$-4-(4-CF$_3$-Ph)Ph	-OH	-CH$_2$-NH-(CH$_2$)$_3$-(imidazol-1-yl)
334	-CH$_2$CH$_2$-NHSO$_2$-(CH$_2$)$_9$CH$_3$	-OH	-CH$_2$-NH-(6-oxo-[1,3]oxazinan-3-yl)
335	-CH$_2$CH$_2$-NH-(CH$_2$)$_8$CH$_3$	-OH	-CH$_2$-*N*-(*N*-CH$_3$-D-glucamine)
336	-CH$_2$CH$_2$-NHSO$_2$-(CH$_2$)$_9$CH$_3$	-OH	-CH$_2$-NH-(CH$_2$)$_3$-(imidazol-1-yl)
337	-H	-*N*-(D-glucosamine)	-CH$_2$-NH-CH$_2$CH$_2$-NHSO$_2$-(CH$_2$)$_{11}$CH$_3$

No.	R^{15} (W = -NH_2)	R^{22}	R^{23}
338	-H	-OH	-CH_2-NH-CH_2CH_2-S-$(CH_2)_7CH_3$
339	-H	-OH	-CH_2-NH-CH_2CH_2-S-$(CH_2)_8CH_3$
340	-H	-OH	-CH_2-NH-CH_2CH_2-$NHSO_2$-$(CH_2)_8CH_3$
341	-H	-OH	-CH_2-NH-CH_2CH_2-S-$(CH_2)_9CH_3$
342	-H	-OH	-CH_2-NH-CH_2CH_2-$NHSO_2$-$(CH_2)_7CH_3$
343	-CH_2CH_2-NH-CH_2-4-(4-CF_3-Ph)Ph	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)
344	-H	-OH	-CH_2-NH-CH_2CH_2-S-$(CH_2)_{11}CH_3$
345	-H	-OH	-CH_2-NH-CH_2CH_2-$NHSO_2$-$(CH_2)_{11}CH_3$
346	-H	-OH	-CH_2-NH-CH_2CH_2-S-$(CH_2)_6$Ph
347	-H	-OH	-CH_2-NH-CH_2CH_2-S-$(CH_2)_8$Ph
348	-H	-OH	-CH_2-NH-CH_2CH_2-S-$(CH_2)_{10}$Ph
349	-H	-OH	-CH_2-NH-CH_2CH_2-S-CH_2-4-(4-CF_3-Ph)Ph
350	-CH_2CH_2-S-$(CH_2)_8$Ph	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)
351	-H	-OH	-CH_2-NH-CH_2CH_2-SO_2-$(CH_2)_{11}CH_3$

No.	R^{15} (W = -NH_2)	R^{22}	R^{23}
352	-CH_2CH_2-S-$(CH_2)_8CH_3$	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)

Ph = phenyl

Table IV



VI

No.	R^{15} (R^{23} = H, unless otherwise indicated; W = -NH_2)	R^{22}	R^{27}
353	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-H
354	-H	-OH	-CH_2CH_2-NH-$(CH_2)_9CH_3$
355	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-CH_2CH_2-NH-$(CH_2)_9CH_3$
356	-CH_2CH_2-NH-$(CH_2)_9CH_3$ R^{23} = -CH_2-*N*-(*N*-CH_3-D-glucamine)	-OH	-H
357	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-*N*-(D-glucosamine)	-H
358	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-$(CH_2)_3CH(CH_3)_2$
359	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)$CH_2CH_2CH(CH_3)_2$
360	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)$CH(NH_2)(CH_2)_4NH_2$ (R isomer)
361	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)$CH(NH_2)(CH_2)_4NH_2$ (S isomer)
362	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)$CH(NH_2)(CH_2)_2$COOH (R isomer)
363	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(NH)NH_2
364	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)$CH(NH_2)CH_2$-(imidazol-4-yl) (R isomer)
365	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)$CH(NH_2)CH_2$-COOH (R isomer)

No.	R^{15} (R^{23} = H, unless otherwise indicated; W = -NH_2)	R^{22}	R^{27}
366	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)$CH(NH_2)CH(CH_3)CH_2CH_3$ (S isomer)
367	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)$NHCH_2CH(CH_3)_2$
368	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(NH)$CH_2CH(CH_3)_2$
369	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)$CH(NH_2)CH_2$-Ph (R isomer)
370	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH_2NHCH_3
371	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)$CH(NH_2)CH_2$-3-HO-Ph
372	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)$CH(NH_2)CH_2$-3-HO-Ph
373	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)-2-[$PhCH(CH_3)NHC(O)$-]Ph (R isomer)
374	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)-[1-PhC(O)-2-oxoimidazolidin-5-yl] (S isomer)
375	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH_2-(1-HO-cycloprop-1-yl)
376	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH_2-(naphth-2-yl)
377	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)$(CH_2)_9$-OH
378	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)-2,4-di-HO-Ph
379	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)-2,6-di-HO-3-pyridyl

No.	R^{15} (R^{23} = H, unless otherwise indicated; W = -NH_2)	R^{22}	R^{27}
380	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH_2-O-CH_2CH_2-O-$CH_2CH_2OCH_3$
381	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)$CH_2CH(Ph)_2$
382	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH_2-3-HO-Ph
383	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH_2-NHC(O)-3-CH_3-Ph
384	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH_2CH_2-O-Ph
385	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH_2CH_2-3-pyridyl
386	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)$CH_2CH_2CH_2$-4-CH_3O-Ph
387	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)-(3H-benzotriazol-5-yl)
388	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)-[1-$(CH_3)_3$COC(O)-pyrrolidin-2-yl) (S isomer)
389	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)$CH_2CH_2CH_2$-cyclohexyl
390	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)-(1H-indol-2-yl)
391	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH_2NHC(O)-furan-2-yl
392	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH(NHC(O)CH_3)CH_2-4-HO-Ph (S isomer)
393	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH_2NHC(O)CH=CH-furan-2-yl (*trans*)

No.	R^{15} (R^{23} = H, unless otherwise indicated; W = -NH_2)	R^{22}	R^{27}
394	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)-(1-CH_3CH_2-7-CH_3-4-oxo-1,4-dihydro[1,8]naphthyridin-3-yl)
395	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)-2,3,4,5,6-penta-F-Ph
396	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)-(1,3-benzodioxol-5-yl)
397	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH_2-(4-oxo-2-thiooxothiazolidin-3-yl)
398	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)-(3,4,5-tri-HO-cyclohex-1-enyl)
399	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH_2CH_2C(O)NH_2
400	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH_2-(5-CH_3-2,4-dioxo-3,4-dihydropyrimidin-1-yl)
401	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH(NH_2)CH$(CH_3)_2$ (R isomer)
402	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH(NH_2)CH_2C(O)-(2-H_2N-Ph)
403	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH_2-NH_2
404	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH(NHCH_3)CH_2CH$(CH_3)_2$ (S isomer)
405	-CH_2CH_2-NH-$(CH_2)_9CH_3$	-OH	-C(O)CH(NH_2)CH_2CH$(CH_3)_2$ (S isomer)

Ph = phenyl

In the preferred compounds illustrated in the above Tables, *W* is amino ($-NH_2$). Other preferred compounds of this invention include each of the compounds illustrated in the Tables above in which W is $-N_3$, $-NHNH_2$, $-NHC(O)CF_3$, $-NHC(O)CH_2NH_2$, $-NHC(S)NHCH_3$, $-SCH(CH_3)_2$, $-SCH_2COOH$, $-NH(CH_2)_9CH_3$, $-NHC(O)(CH_2)_{12}CH_3$, imidazol-1-yl, -S-(1-CH_3-tetrazol-5-yl), -S-(3-H_2N-1,2,4-triazol-5-yl), -S-(5-H_2N-1,3,4-thiadiazol-2-yl), -S-(3-H_2NNH-4-H_2N-1,2,4-triazol-5-yl), -NHC(O)-(thiophen-2-yl), -S-(phenyl), -S-(4-Br-phenyl), -S-(3-Cl-phenyl), -S-(4-CF_3-pyrimidin-2-yl), -S-(4-H_2N-pyrimidin-2-yl), -S-(4,6-di-H_2N-pyrimidin-2-yl), -S-(4-HO-6-H_2N-pyrimidin-2-yl), -S-(4-HO-6-CH_3-pyrimidin-2-yl), -S-(6-azathymin-2-yl), $-NHCH_2$-(2-HO-5-Cl-phenyl), -NHC(O)-(2-I-phenyl), $-S(O)_2$-(2,4,6-tri-CH_3-phenyl), -S-(5-CH_3O-benzimidazol-2-yl), -S-(5-Cl-benzimidazol-2-yl), -NHC(O)-(quinoxalin-2-yl), $-NHCH_2$-[4-(4-Cl-phenyl)phenyl], -NHC(O)-[4-(4-Cl-phenyl)phenyl], $-NHCH_2$-[5-(4-Cl-phenyl)furan-2-yl], -S-(5-phenyl-1,3,4-oxadiazol-2-yl), -S-[1-(4-HO-phenyl-)tetrazol-5-yl], -S-(4,5-diphenyloxazol-2-yl), or $-OS(O)_2$-(pyren-2-yl), and pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to novel derivatives of glycopeptide antibiotics and to pharmaceutical compositions and methods employing such glycopeptide derivatives. When describing the compounds, compositions and methods of this invention, the following terms have the following meanings, unless otherwise indicated.

Definitions

The term "alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms, and even more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, *n*-decyl, tetradecyl, and the like.

The term "substituted alkyl" refers to an alkyl group as defined above, having from 1 to 8 substituents, preferably 1 to 5 substitutents, and more preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "alkylene" refers to a diradical of a branched or unbranched saturated hydrocarbon chain, preferably having from 1 to 40 carbon atoms, preferably 1-10 carbon atoms, more preferably 1-6 carbon atoms. This term is exemplified by groups such as methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), the propylene isomers (e.g., $-CH_2CH_2CH_2-$ and $-CH(CH_3)CH_2-$) and the like.

The term "substituted alkylene" refers to an alkylene group, as defined above, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl. Additionally, such substituted alkylene groups include those where 2 substituents on the alkylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group. Preferably such fused groups contain from 1 to 3 fused ring structures. Additionally, the term substituted

alkylene includes alkylene groups in which from 1 to 5 of the alkylene carbon atoms are replaced with oxygen, sulfur or -NR- where R is hydrogen or alkyl. Examples of substituted alkylenes are chloromethylene (-CH(Cl)-), aminoethylene (-$CH(NH_2)$CH2-), 2-carboxypropylene isomers (-$CH_2CH(CO_2H)CH_2$-), ethoxyethyl (-CH_2CH_2 O-CH_2CH_2-) and the like.

The term "alkaryl" refers to the groups -alkylene-aryl and -substituted alkylene-aryl where alkylene, substituted alkylene and aryl are defined herein. Such alkaryl groups are exemplified by benzyl, phenethyl and the like.

The term "alkoxy" refers to the groups alkyl-O-, alkenyl-O-, cycloalkyl-O-, cycloalkenyl-O-, and alkynyl-O-, where alkyl, alkenyl, cycloalkyl, cycloalkenyl, and alkynyl are as defined herein. Preferred alkoxy groups are alkyl-O- and include, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

The term "substituted alkoxy" refers to the groups substituted alkyl-O-, substituted alkenyl-O-, substituted cycloalkyl-O-, substituted cycloalkenyl-O-, and substituted alkynyl-O- where substituted alkyl, substituted alkenyl, substituted cycloalkyl, substituted cycloalkenyl and substituted alkynyl are as defined herein.

The term "alkylalkoxy" refers to the groups -alkylene-O-alkyl, alkylene-O-substituted alkyl, substituted alkylene-O-alkyl and substituted alkylene-O-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylalkoxy groups are alkylene-O-alkyl and include, by way of example, methylenemethoxy (-CH_2OCH_3), ethylenemethoxy (-$CH_2CH_2OCH_3$), *n*-propylene-*iso*-propoxy (-$CH_2CH_2CH_2OCH(CH_3)_2$), methylene-*t*-butoxy (-CH_2-O-$C(CH_3)_3$) and the like.

The term "alkylthioalkoxy" refers to the group -alkylene-S-alkyl, alkylene-S-substituted alkyl, substituted alkylene-S-alkyl and substituted alkylene-S-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylthioalkoxy groups are alkylene-S-alkyl and include, by way of example, methylenethiomethoxy (-CH_2SCH_3), ethylenethiomethoxy (-$CH_2CH_2SCH_3$), *n*-propylene-*iso*-thiopropoxy

($-CH_2CH_2CH_2SCH(CH_3)_2$), methylene-*t*-thiobutoxy ($-CH_2SC(CH_3)_3$) and the like.

The term "alkenyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. Preferred alkenyl groups include ethenyl ($-CH=CH_2$), *n*-propenyl ($-CH_2CH=CH_2$), isopropenyl ($-C(CH_3)=CH_2$), and the like.

The term "substituted alkenyl" refers to an alkenyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "alkenylene" refers to a diradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. This term is exemplified by groups such as ethenylene (-CH=CH-), the propenylene isomers (e.g., $-CH_2CH=CH-$ and $-C(CH_3)=CH-$) and the like.

The term "substituted alkenylene" refers to an alkenylene group as defined above having from 1 to 5 substituents, and preferably from 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy,

heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl and -SO_2-heteroaryl. Additionally, such substituted alkenylene groups include those where 2 substituents on the alkenylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkenylene group.

The term "alkynyl" refers to a monoradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 20 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynyl groups include ethynyl (-C≡CH), propargyl (-CH_2C≡CH) and the like.

The term "substituted alkynyl" refers to an alkynyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl and -SO_2-heteroaryl.

The term "alkynylene" refers to a diradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynylene groups include ethynylene (-C≡C-), propargylene (-CH_2C≡C-) and the like.

The term "substituted alkynylene" refers to an alkynylene group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted

cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl

The term "acyl" refers to the groups HC(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, cycloalkenyl-C(O)-, substituted cycloalkenyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)- where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "acylamino" or "aminocarbonyl" refers to the group -C(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic or where both R groups are joined to form a heterocyclic group (e.g., morpholino) wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "aminoacyl" refers to the group -NRC(O)R where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "aminoacyloxy" or "alkoxycarbonylamino" refers to the group -NRC(O)OR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, aryl-C(O)O-, heteroaryl-C(O)O-, and heterocyclic-C(O)O- wherein alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like. Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with from 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, aminoacyloxy, oxyacylamino, sulfonamide, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

The term "aryloxy" refers to the group aryl-O- wherein the aryl group is as defined above including optionally substituted aryl groups as also defined above.

The term "arylene" refers to the diradical derived from aryl (including substituted aryl) as defined above and is exemplified by 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,2-naphthylene and the like.

The term "amino" refers to the group $-NH_2$.

The term "substituted amino" refers to the group -NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic provided that both R's are not hydrogen.

"Amino acid" refers to any of the naturally occurring amino acids, as well as synthetic analogs and derivatives thereof. α-Amino acids comprise a carbon atom to which is bonded an amino group, a carboxy group, a hydrogen atom, and a distinctive group referred to as a "side chain". The side chains of naturally occurring

amino acids are well known in the art and include, for example, hydrogen (e.g., as in glycine), alkyl (e.g., as in alanine, valine, leucine, isoleucine, proline), substituted alkyl (e.g., as in threonine, serine, methionine, cysteine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, and lysine), alkaryl (e.g., as in phenylalanine and tryptophan), substituted arylalkyl (e.g., as in tyrosine), and heteroarylalkyl (e.g., as in histidine).

The term "carboxyalkyl" or "alkoxycarbonyl" refers to the groups "-C(O)O-alkyl", "-C(O)O-substituted alkyl", "-C(O)O-cycloalkyl", "-C(O)O-substituted cycloalkyl", "-C(O)O-alkenyl", "-C(O)O-substituted alkenyl", "-C(O)O-alkynyl" and "-C(O)O-substituted alkynyl" where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl and substituted alkynyl alkynyl are as defined herein.

The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

The term "substituted cycloalkyl" refers to cycloalkyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 20 carbon atoms having a single cyclic ring and at least one point of internal

unsaturation. Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl and the like.

The term "substituted cycloalkenyl" refers to cycloalkenyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl and -SO_2-heteroaryl.

The term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

"Haloalkyl" refers to alkyl as defined herein substituted by 1-4 halo groups as defined herein, which may be the same or different. Representative haloalkyl groups include, by way of example, trifluoromethyl, 3-fluorododecyl, 12,12,12-trifluorododecyl, 2-bromooctyl, 3-bromo-6-chloroheptyl, and the like.

The term "heteroaryl" refers to an aromatic group of from 1 to 15 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring).

Unless otherwise constrained by the definition for the heteroaryl substituent, such heteroaryl groups can be optionally substituted with 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl,

-SO_2-substituted alkyl, -SO_2-aryl, -SO_2-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl). Preferred heteroaryls include pyridyl, pyrrolyl and furyl.

"Heteroarylalkyl" refers to (heteroaryl)alkyl- where heteroaryl and alkyl are as defined herein. Representative examples include 2-pyridylmethyl and the like.

The term "heteroaryloxy" refers to the group heteroaryl-O-.

The term "heteroarylene" refers to the diradical group derived from heteroaryl (including substituted heteroaryl), as defined above, and is exemplified by the groups 2,6-pyridylene, 2,4-pyridiylene, 1,2-quinolinylene, 1,8-quinolinylene, 1,4-benzofuranylene, 2,5-pyridnylene, 2,5-indolenyl and the like.

The term "heterocycle" or "heterocyclic" refers to a monoradical saturated unsaturated group having a single ring or multiple condensed rings, from 1 to 40 carbon atoms and from 1 to 10 hetero atoms, preferably 1 to 4 heteroatoms, selected from nitrogen, sulfur, phosphorus, and/or oxygen within the ring. Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocyclic groups can be optionally substituted with 1 to 5, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl and -SO_2-heteroaryl. Such heterocyclic groups can have a single ring or multiple condensed rings. Preferred heterocyclics include morpholino, piperidinyl, and the like.

Examples of nitrogen heterocycles and heteroaryls include, but are not limited to, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine,

indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, morpholino, piperidinyl, tetrahydrofuranyl, and the like as well as N-alkoxy-nitrogen containing heterocycles.

Another class of heterocyclics is known as "crown compounds" which refers to a specific class of heterocyclic compounds having one or more repeating units of the formula $[-(CH_2-)_aA-]$ where a is equal to or greater than 2, and A at each separate occurrence can be O, N, S or P. Examples of crown compounds include, by way of example only, $[-(CH_2)_3-NH-]_3$, $[-((CH_2)_2-O)_4-((CH_2)_2-NH)_2]$ and the like. Typically such crown compounds can have from 4 to 10 heteroatoms and 8 to 40 carbon atoms.

The term "heterocyclooxy" refers to the group heterocyclic-O-.

The term "thioheterocyclooxy" refers to the group heterocyclic-S-.

The term "heterocyclene" refers to the diradical group formed from a heterocycle, as defined herein, and is exemplified by the groups 2,6-morpholino, 2,5-morpholino and the like.

The term "oxyacylamino" or "aminocarbonyloxy" refers to the group -OC(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "saccharide group" refers to an oxidized, reduced or substituted saccharide monoradical covalently attached to the glycopeptide or other compound via any atom of the saccharide moiety, preferably via the aglycone carbon atom. Respresentative saccharides include, by way of illustration, hexoses such as D-glucose, D-mannose, D-xylose, D-galactose, vancosamine, 3-desmethyl-vancosamine, 3-epi-vancosamine, 4-epi-vancosamine, acosamine, actinosamine, daunosamine, 3-epi-daunosamine, ristosamine, N-methyl-D-glucamine, D-glucuronic acid, *N*-acetyl-D-glucosamine, *N*-acetyl-D-galactosamine, sialyic acid,

iduronic acid, L-fucose, and the like; pentoses such as D-ribose or D-arabinose; ketoses such as D-ribulose or D-fructose; disaccharides such as 2-O-(α-L-vancosaminyl)-β-D-glucopyranose, 2-O-(3-desmethyl-α-L-vancosaminyl)-β-D-glucopyranose, sucrose, lactose, or maltose; derivatives such as acetals, amines, acylated, sulfated and phosphorylated sugars; oligosaccharides having from 2 to 10 saccharide units. For the purposes of this definition, these saccharides are referenced using conventional three letter nomenclature and the saccharides can be either in their open or preferably in their pyranose form.

The term "amino-containing saccharide group" refers to a saccharide group having an amino substituent. Representative amino-containing saccharides include L-vancosamine, 3-desmethyl-vancosamine, 3-epi-vancosamine, 4-epi-vancosamine, acosamine, actinosamine, daunosamine, 3-epi-daunosamine, ristosamine, *N*-methyl-D-glucamine and the like.

The term "spiro-attached cycloalkyl group" refers to a cycloalkyl group attached to another ring via one carbon atom common to both rings.

The term "sulfonamide" refers to a group of the formula $-SO_2NRR$, where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "thiol" refers to the group -SH.

The term "thioalkoxy" refers to the group -S-alkyl.

The term "substituted thioalkoxy" refers to the group -S-substituted alkyl.

The term "thioaryloxy" refers to the group aryl-S- wherein the aryl group is as defined above including optionally substituted aryl groups also defined above.

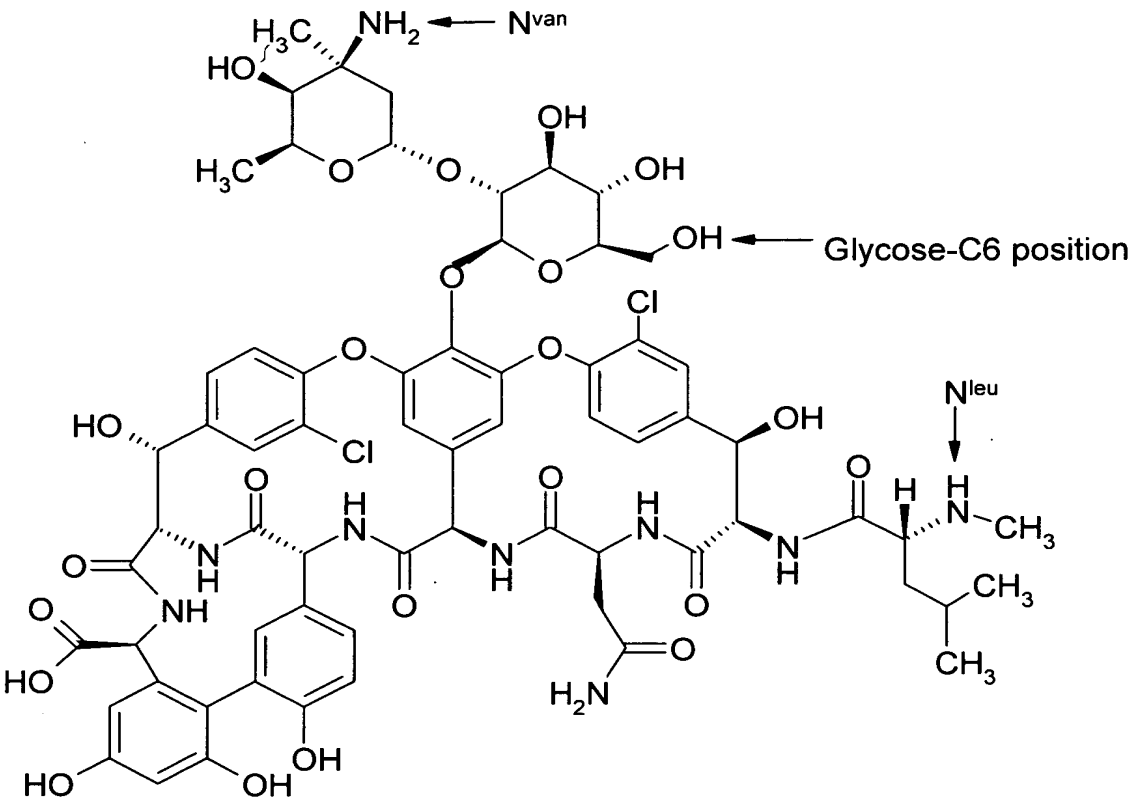
The term "thioheteroaryloxy" refers to the group heteroaryl-S- wherein the heteroaryl group is as defined above including optionally substituted aryl groups as also defined above.

As to any of the above groups which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-

feasible. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these compounds.

"Glycopeptide" refers to heptapeptide (dalbaheptide) antibiotics, characterized by a multi-ring peptide core optionally substituted with saccharide groups, such as vancomycin. Examples of glycopeptides included in this definition may be found in "Glycopeptides Classification, Occurrence, and Discovery", by Raymond C. Rao and Louise W. Crandall, ("Drugs and the Pharmaceutical Sciences"Volume 63, edited by Ramakrishnan Nagarajan, published by Marcal Dekker, Inc.), which is hereby incorporated by reference in its entirety. Representative glycopeptides include those identified as A477, A35512, A40926, A41030, A42867, A47934, A80407, A82846, A83850 ,A84575, AB-65, Actaplanin, Actinoidin, Ardacin, Avoparcin, Azureomycin, Balhimycin, Chloroorientiein, Chloropolysporin, Decaplanin, *N*-demethylvancomycin, Eremomycin, Galacardin, Helvecardin, Izupeptin, Kibdelin, LL-AM374, Mannopeptin, MM45289, MM47756, MM47761, MM49721, MM47766, MM55260, MM55266, MM55270, MM56597, MM56598, OA-7653, Orenticin, Parvodicin, Ristocetin, Ristomycin, Synmonicin, Teicoplanin, UK-68597, UK-69542, UK-72051, Vancomycin, and the like. The term "glycopeptide" as used herein is also intended to include the general class of peptides disclosed above on which the sugar moiety is absent, i.e. the aglycone series of glycopeptides. For example, removal of the disaccharide moiety appended to the phenol on vancomycin by mild hydrolysis gives vancomycin aglycone. Also within the scope of the invention are glycopeptides that have been further appended with additional saccharide residues, especially aminoglycosides, in a manner similar to vancosamine; and glyclopeptides in which the *N*-terminal amino acid has been removed.

"Vancomycin" refers to a glycopeptide antibiotic having the formula:



When describing vancomycin derivatives, the term "N^{van}-" indicates that a substituent is covalently attached to the amino group of the vacosamine moiety of vacomycin. Similarly, the term "N^{leu}-" indicates that a substituent is covalently attached to the amino group of the leucine moiety of vancomycin. The glucose-C6 position of vancomycin is also indicated above.

"Cyclodextrin" refers to cyclic molecules containing six or more α-D-glucopyranose units linked at the 1,4 positions by α linkages as in amylose. β-Cyclodextrin or cycloheptaamylose contains seven α-D-glucopyranose units. As used herein, the term "cyclodextrin" also includes substituted cyclodextrin derivatives such as hydroxypropyl and sulfobutyl ether cyclodextrins. Such derivatives are described for example, in U.S. Patent Nos. 4,727,064 and 5,376,645, the disclosures of which are incorporated herein by reference in their entirety.

Additionally, hydropropyl-β-cyclodextrin and sulfobutyl-β-cyclodextrin are commercially available.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted" means that a group may or may not be substituted with the described substitutent.

"Transglycosylase enzyme substrate" as used herein denotes the molecular target of the transglycosylase enzyme. The substrate binds to the enzyme and eventually results in synthesis of the bacterial cell wall. The action of this enzyme is inhibited by a ligand domain that binds to the enzyme substrate. A ligand such as vancomycin binds to this substrate and in effect "sequesters" the substrate to prevent its recognition by the enzyme and subsequent use in the construction of the bacterial cell wall.

"Potency" as used herein refers to the minimum concentration at which a compound or ligand is able to achieve a desirable biological or therapeutic effect. The potency of a compound or ligand is typically proportional to its affinity for its binding site. In some cases, the potency may be non-linearly correlated with its affinity

As used herein, the terms "inert organic solvent" or "inert solvent" or "inert diluent" mean a solvent or diluent which is essentially inert under the conditions of the reaction in which it is employed as a solvent or diluent. Representative examples of materials which may be used as inert solvents or diluents include, by way of illlustration, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform ("$CHCl_3$"), methylene chloride (or dichloromethane or "CH_2C1_2), diethyl ether, ethyl acetate, acetone, methylethyl ketone, methanol, ethanol, propanol, isopropanol, tert-butanol, dioxane, pyridine, and the like. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert solvents.

"Pharmaceutically acceptable salt" means those salts which retain the biological effectiveness and properties of the parent compounds and which are not biologically or otherwise harmful as the dosage administered. The compounds of this invention are capable of forming both acid and base salts by virtue of the presence of amino and carboxyl groups respectively.

Pharmaceutically acceptable base addition salts may be prepared from inorganic and organic bases. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, substituted amines including naturally-occurring substituted amines, and cyclic amines, including isopropylamine, trimethyl amine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, and N-ethylpiperidine. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example carboxylic acid amides, including carboxamides, lower alkyl carboxamides, di(lower alkyl) carboxamides, and the like.

Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

The compounds of this invention typically contain one or more chiral centers. Accordingly, this invention is intended to include racemic mixtures, diasteromers, enantiomers and mixture enriched in one or more steroisomer. The scope of the invention as described and claimed encompasses the racemic forms of

the compounds as well as the individual enantiomers and non-racemic mixtures thereof.

The term "treatment" as used herein includes any treatment of a condition or disease in an animal, particularly a mammal, more particularly a human, and includes:

(i) preventing the disease or condition from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it;

(ii) inhibiting the disease or condition, i.e. arresting its development; relieving the disease or condition, i.e. causing regression of the condition; or. relieving the conditions caused by the disease, i.e. symptoms of the disease.

The term "bacterial disease" as used herein refers to all disease states which are generally acknowledged in the art to be usefully treated with a broad spectrum antibacterial in general, and those disease states which have been found to be usefully treated by the specific antibacterials of this invention. Such disease states include, but are not limited to, treatment of a mammal afflicted with pathogenic bacteria, in particular staphylococci (methicillin sensitive and resistant), streptococci (penicillin sensitive and resistant), enterococci (vancomycin sensitive and resistant), and Clostridium difficile

The term "therapeutically effective amount" refers to that amount which is sufficient to effect treatment, as defined herein, when administered to a mammal in need of such treatment. The therapeutically effective amount will vary depending on the subject and disease state being treated, the severity of the affliction and the manner of administration, and may be determined routinely by one of ordinary skill in the art.

The term "protecting group" or "blocking group" refers to any group which, when bound to one or more hydroxyl, thiol, amino, carboxyl or other groups of the compounds, prevents undesired reactions from occurring at these groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl, thio, amino, carboxyl or other group. The particular removable blocking group employed is not critical and preferred removable hydroxyl blocking groups include conventional substituents such as allyl, benzyl, acetyl, chloroacetyl, thiobenzyl, benzylidine, phenacyl, t-butyl-diphenylsilyl and any other group that can be introduced chemically onto a hydroxyl functionality and later

selectively removed either by chemical or enzymatic methods in mild conditions compatible with the nature of the product. Protecting groups are disclosed in more detail in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis" 2nd Ed., 1991, John Wiley and Sons, N.Y.

Preferred removable amino blocking groups include conventional substituents such as t-butyoxycarbonyl (t-BOC), benzyloxycarbonyl (CBZ), fluorenylmethoxycarbonyl (FMOC), allyloxycarbonyl (ALOC) and the like, which can be removed by conventional conditions compatible with the nature of the product.

Preferred carboxyl protecting groups include esters such as methyl, ethyl, propyl, *t*-butyl etc. which can be removed by mild conditions compatible with the nature of the product.

"Biological effect" as used herein includes, but is not limited to, increased affinity, increased selectivity, increased potency, increased efficacy, increased duration of action, decreased toxicity, and the like.

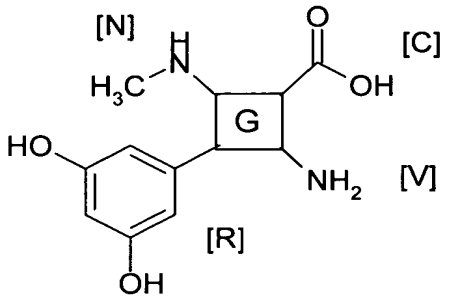
General Synthetic Procedures

The glycopeptide compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

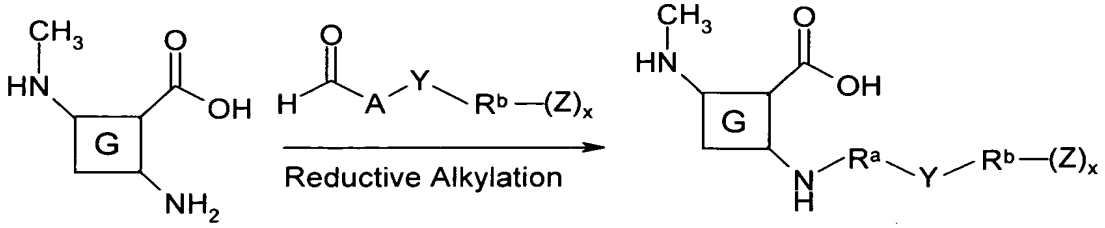
Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups,

and their introduction and removal, are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York, 1999, and references cited therein.

In the following reaction schemes, the glycopeptide compounds are depicted in a simplified form as a box "G" that shows the carboxy terminus labeled [C], the vancosamine amino terminus labeled [V], the "non-saccharide" amino terminus (leucine amine moiety) labeled [N], and optionally, the resorcinol moiety labeled [R] as follows:



In one preferred embodiment, the glycopeptide compounds of the present invention are prepared by first reductively alkylating a glycopeptide as shown in the following reaction:



where A represents R^a minus one carbon atom and R^a, R^b, Y, Z and x are as defined herein. This reaction is typically conducted by first contacting one equivalent of a glycopeptide, such as vancomycin, with an excess, preferably from 1.1 to 1.3

equivalents, of the desired aldehyde in the presence of an excess, preferably about 2.0 equivalents, of a tertiary amine, such as diisopropylethylamine (DIPEA) and the like. This reaction is typically conducted in an inert diluent, such as DMF, at ambient temperature for about 1 to 2 hours until formation of the corresponding imine and/or hemiaminal is substantially complete. The resulting imine and/or hemiaminal is typically not isolated, but is reacted *in situ* with a metal hydride reducing agent, such as sodium cyanoborohydride and the like, to afford the corresponding amine. This reaction is typically conducted by contacting the imine and/or hemiaminal with an excess, preferably about 3 equivalents, of trifluoroacetic acid and then with about 1 to 1.2 equivalents of the reducing agent at ambient temperature in methanol. The resulting alkylated product is readily purified by conventional procedures, such as reverse-phase HPLC. Surprisingly, by forming the imine and/or hemiaminal in the presence of a trialkyl amine and contacting the imine and/or hemiaminal with trifluoroacetic acid before the reducing agent, the selectivity for the reductive alkylation reaction is greatly improved, i.e., reductive alkylation at the amino group of the saccharide (e.g., vancosamine) is favored over reductive alkylation at the *N*-terminus (e.g., the leucinyl group) by at least 10:1, more preferably 20:1.

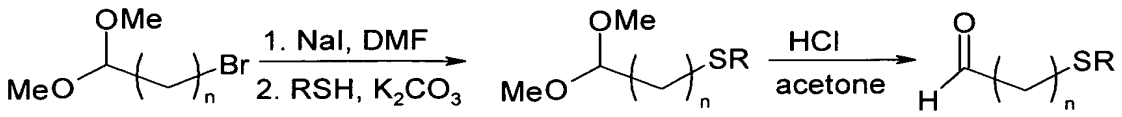
If desired, this reaction can also be conducted in a step-wise manner in which a precursor to the $-R^a-Y-R^b-(Z)_x$ group is first attached the glycopeptide by reductive alkylation, followed by subsequent elaboration of the attached precursor using conventional reagent and procedures to form the $-R^a-Y-R^b-(Z)_x$ group as illustrated below. Additionally, ketones may also be employed in the above-described reductive alkylation reactions to afford α-substituted amines.

Any glycopeptide having an amino group may be employed in these reductive alkylation reactions. Such glycopeptides are well-known in the art and are either commercially available or may be isolated using conventional procedures. Suitable glycopeptides are disclosed, by way of example, in U.S. Patent Nos. 3,067,099; 3,338,786; 3,803,306; 3,928,571; 3,952,095; 4,029,769; 4,051,237; 4,064,233; 4,122,168; 4,239,751; 4,303,646; 4,322,343; 4,378,348; 4,497,802;

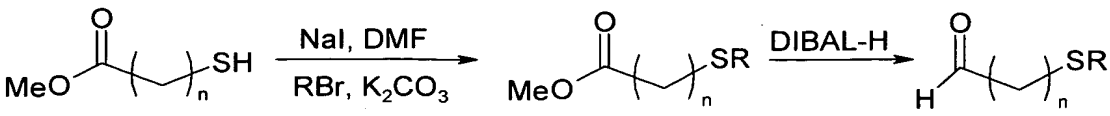
4,504,467; 4,542,018; 4,547,488; 4,548,925; 4,548,974; 4,552,701; 4,558,008; 4,639,433; 4,643,987; 4,661,470; 4,694,069; 4,698,327; 4,782,042; 4,914,187; 4,935,238; 4,946,941; 4,994,555; 4,996,148; 5,187,082; 5,192,742; 5,312,738; 5,451,570; 5,591,714; 5,721,208; 5,750,509; 5,840,684; and 5,843,889; the disclosures of which are incorporated herein by reference in their entirety. Preferably, the glycopeptide employed in the above reaction is vancomycin.

The aldehydes and ketones employed in the reactive alkylation reaction are also well-known in the art and are either commercially available or can be prepared by conventional procedures using commercially available starting materials and conventional reagents. Typically, such materials are prepared by conventional coupling of, for example, functionalized acetals having an amino, thiol, hydroxyl, halo or other substitutent, with an suitable intermediate having a complementary functional group to form sulfides, ethers, amines, sulfonamides and the like. Subsequent hydrolysis of the acetal affords the corresponding aldehyde. Such reactions are well-known in the art and are described, for example, in March, *Advanced Organic Chemistry*, Fourth Edition, John Wiley & Sons, New York (1992), and references cited therein. By way of example, representative syntheses of aldehyde compounds are illustrated in Schemes 1-5:

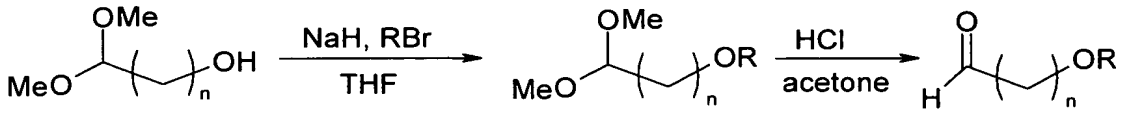
Scheme 1



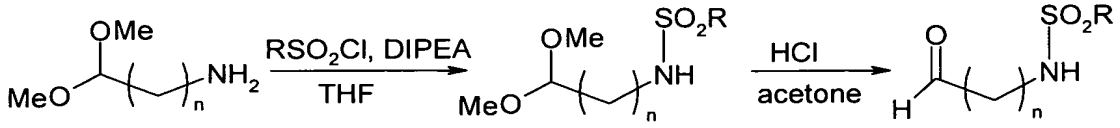
Scheme 2



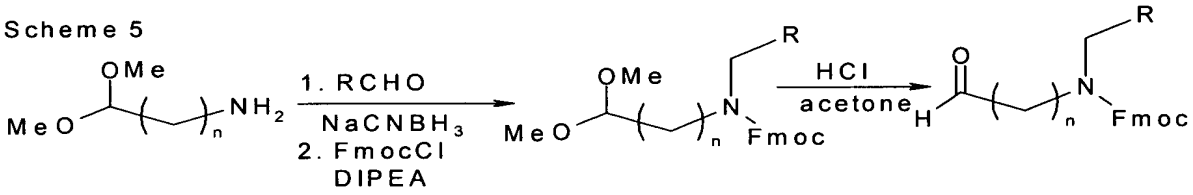
Scheme 3



Scheme 4



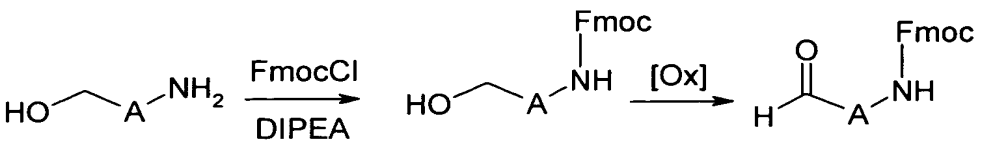
Scheme 5



where R represents $-R^b-(Z)_x$ or -(R^b minus one carbon atom)-$(Z)_x$ (where R^b, Z and *x* are as defined herein).

By way of further illustration, the following schemes describe the synthesis of representative starting materials and intermediates of this invention. For example, Scheme A illustrates a method for preparing an Fmoc-aminoaldehyde **5** from the corresponding aminoalcohol **3**, where A is as defined herein. In this reaction, the aminoalcohol is protected by conventional techniques, for example, by treatment with 9-fluorenylmethyl chloroformate in the presence of base, to yield the Fmoc-protected aminoalcohol **4**. Oxidation by known techniques then provides the aldehyde **5**.

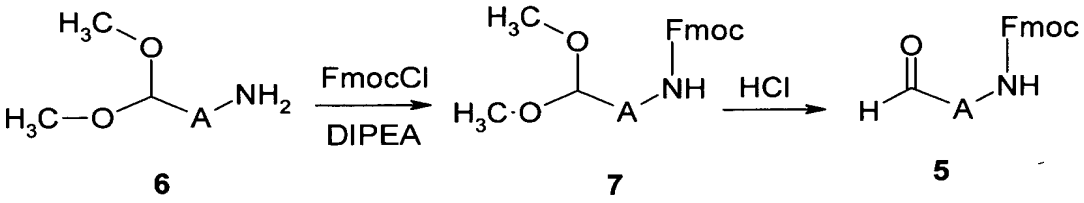
Scheme A



3 **4** **5**

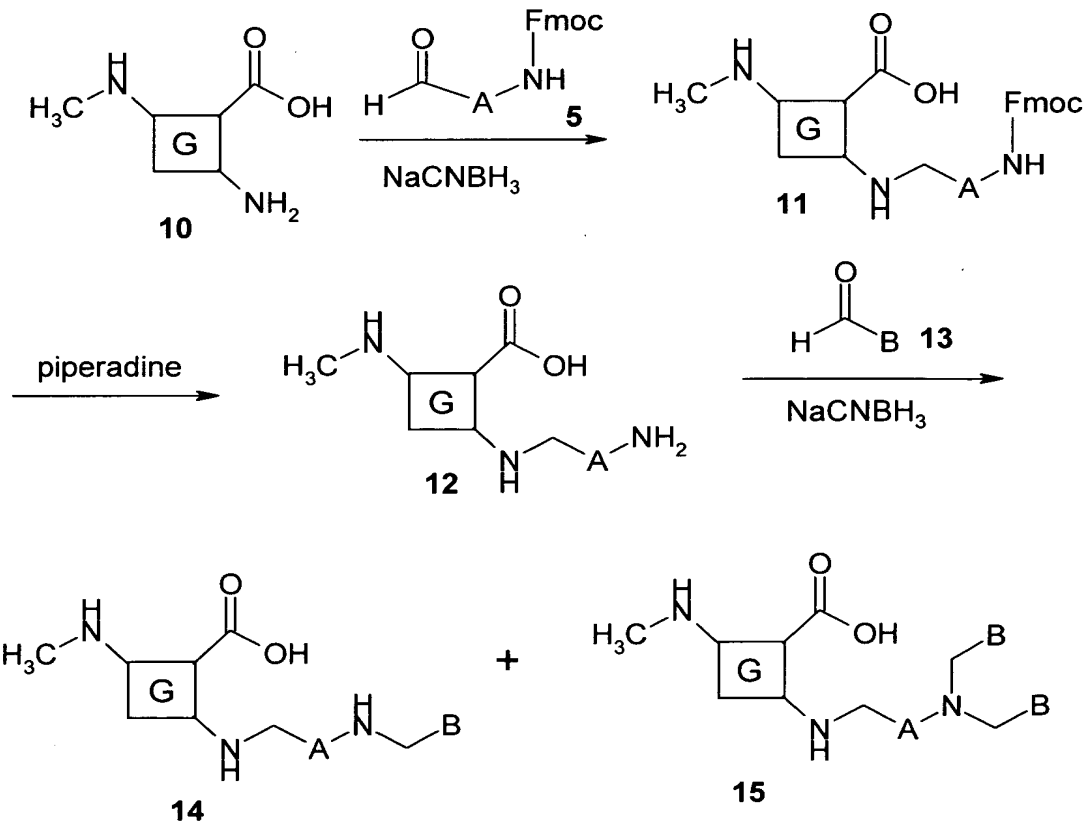
Scheme B illustrates an alternate route to F-moc- protected aminoaldehyde **5**. This route is described in further detail in Sasake, Y., Abe, *J. Chem. Pharm. Bull.* **(1997)**, *45(1)*, 13-17.

Scheme B



The Fmoc-protected aminoaldehyde of formula **5** can then be reacted with a glycopeptide, for example vancomycin, as shown in Scheme C.

Scheme C

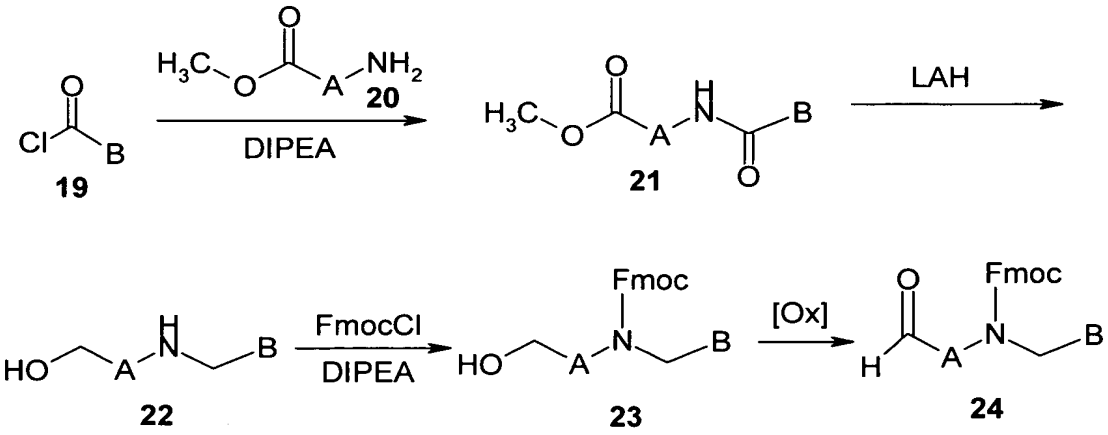


where B represents -(R^b minus one carbon atom)-$(Z)_x$, where R^b, Z and *x* are as defined herein.

This reaction is conducted under reductive alkylation conditions to yield a glycopeptide intermediate **11**. Deprotection of **11** with piperidine yields the corresponding the glycopeptide **12** having a primary amino group. Reaction of **12** with aldehyde **13** under standard reductive alkylation conditions gives glycopeptide derivative **14** and the corresponding bis-adduct **15**, which are separated by conventional techniques, such as HPLC.

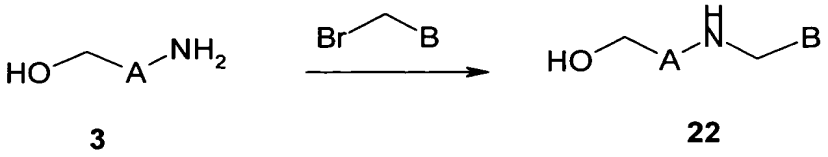
Scheme D illustrates a method for preparing an Fmoc protected aminoaldehyde **24**. In this scheme, reaction of acid chloride **19** with aminoester **20** under conventional amide coupling conditions gives amidoester **21**. Reduction of the both the ester and amide moieties using a metal hydride reducing agent, such as lithium aluminum hydride (LAH) gives aminoalcohol **22**. Protection and oxidation, as in Scheme A, yields an aldehyde of formula **24**.

Scheme D



Alternatively, aldehyde **24** can be prepared as shown in Scheme D'. In this reaction, direct alkylation of amino alcohol **3** under conventional amine alkylation conditions gives amino alcohol **22**, which can then be used as described above in Scheme D.

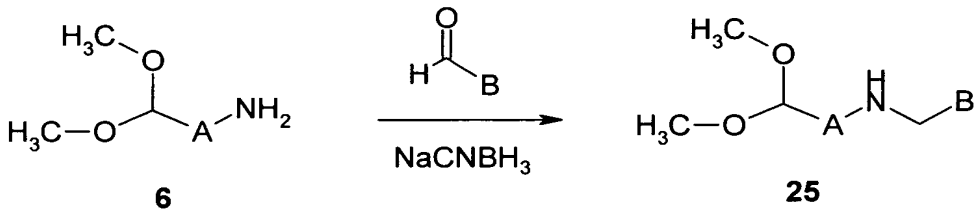
Scheme D'



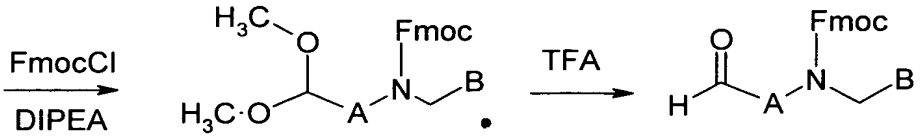
3 22

Scheme E illustrates an alternative method for preparing aldehyde **24**. In this reaction, amino acetal **6** is reductively alkylated to provide **25**. Subsequent protection of the amino group and hydrolysis of the acetal under conventional conditions then provides aldehyde **24**.

Scheme E



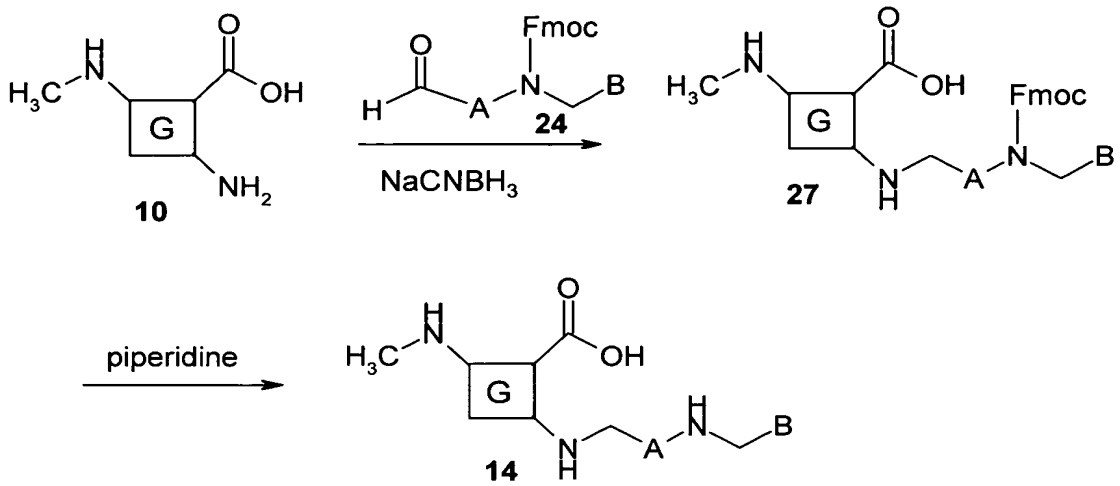
6 25



26 24

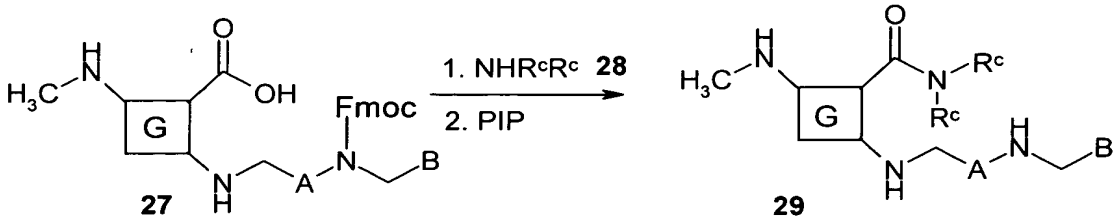
Scheme F illustrates another method for reductive alkylation of a glycopeptide. In this scheme, Fmoc-protected aldehyde **24**, prepared as descrubed above, is reacted with a glycopeptide **10**, such as vancomycin, under reductive alkylation conditions to afford glycopeptide derivative **27**. Subsequent deprotection with piperidine provides glycopeptide derivative **14**.

Scheme F



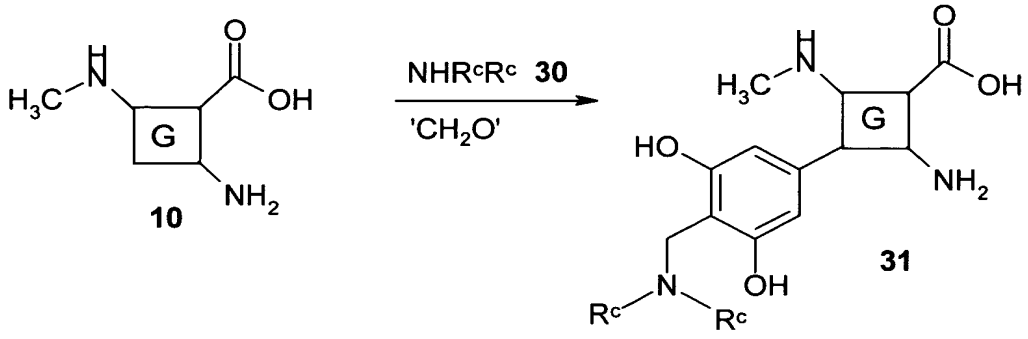
Scheme G illustrates the conversion of the carboxyl group of a glycopeptide derivative, such as vancomycin, into an amide. In this reaction, amine **28** is reacted with a glycopeptide derivative, such as **27**, under standard peptide coupling conditions, for example, PyBOP and HOBT in DMF, to provide amide **29**, after deprotection.

Scheme G



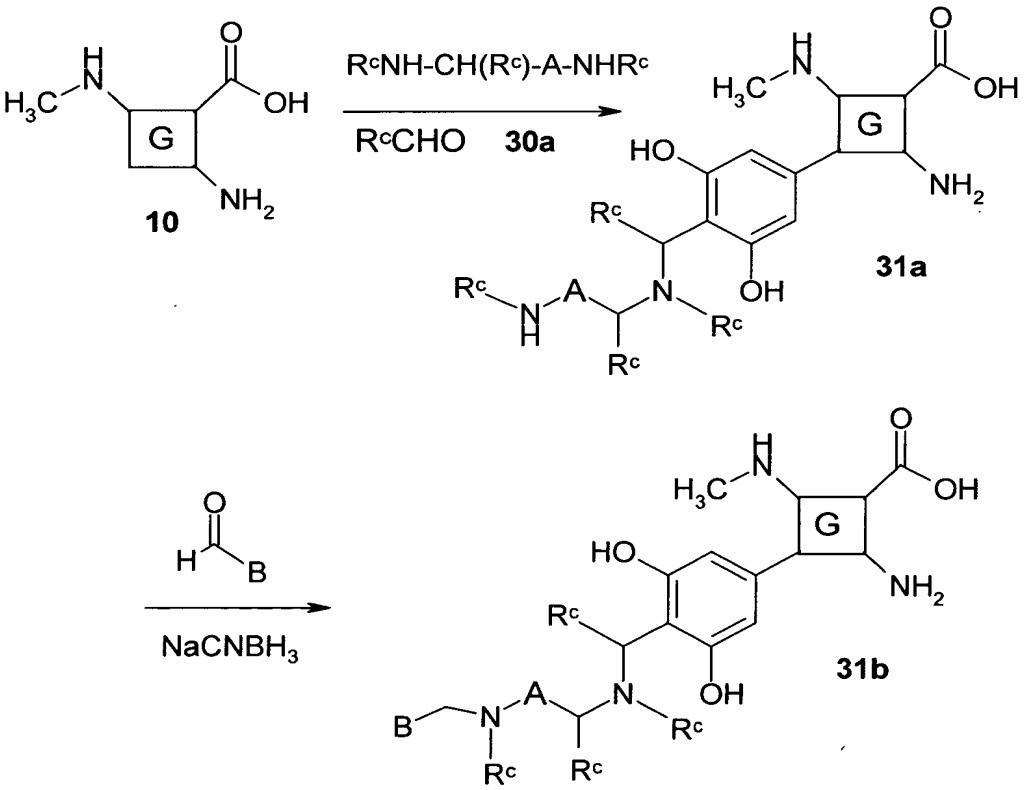
Scheme H illustrates the introduction of an aminoalkyl sidechain at the resorcinol moiety of a glycopeptide, such as vancomycin, via a Mannich reaction. In this reaction, amine **30** and an aldehyde, such as formalin (a source of formaldehyde), are reacted with the glycopeptide under basic conditions to give the glycopeptide derivative **31**.

Scheme H



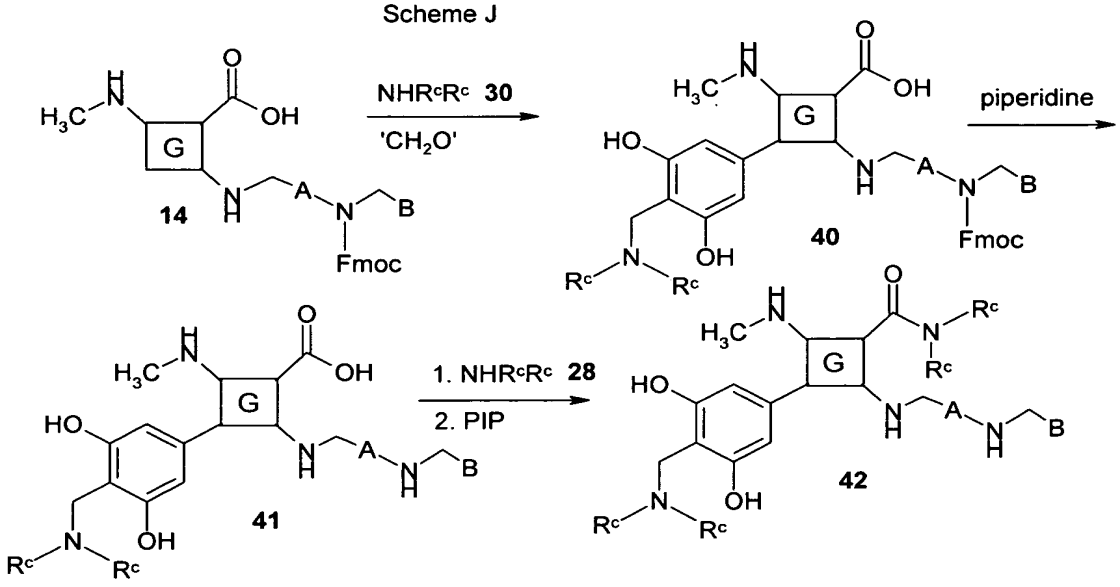
Similarly, Scheme I illustrates a introduction of a substituent of the formula $-R^a-Y-R^b-(Z)_x$ at the resorcinol moiety of a glycopeptide using the Mannich reaction.

Scheme I



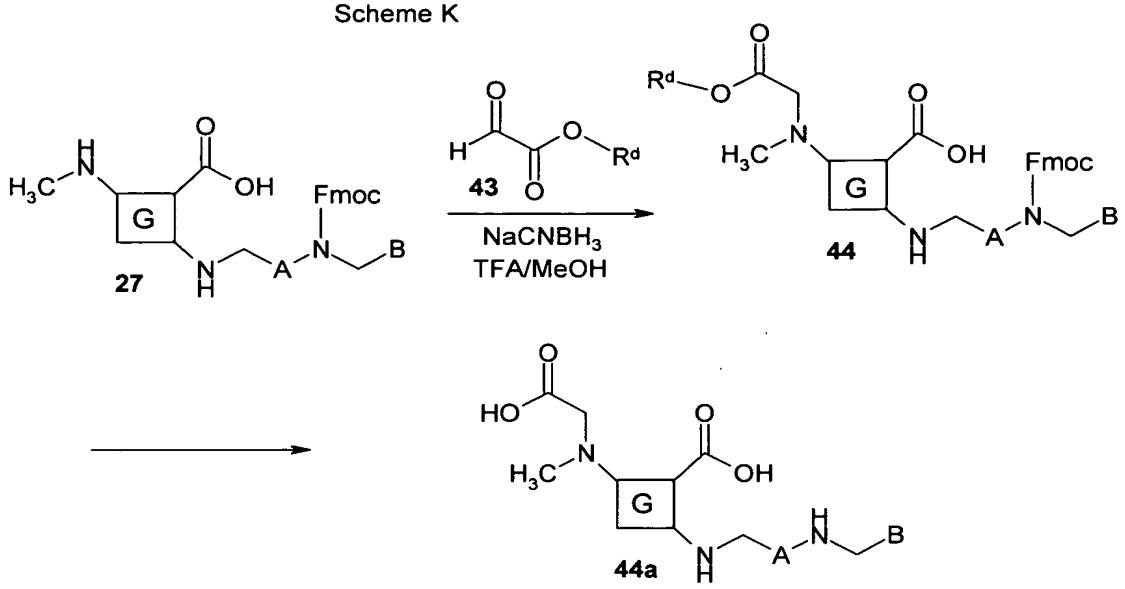
Scheme J illustrates a synthesis of a glycopeptide derivative using several of the reactions described above. In this scheme, glycopeptide derivative **27** is derivatized at the resorcinol moiety using the Mannich reaction described in Scheme H to provide glycopeptide derivative **40**. Deprotection and amide coupling at the carboxyl group, as described in Scheme G, affords glycopeptide derivative **42**.

Scheme J



Scheme K illustrates multiple reductive alkylation reaction of a glycopeptide derivative **27** to afford glycopeptide derivative **44a**.

Scheme K



The substituent at the glucose-C6 position of the compounds of this invention is readily introduced by first converting the naturally-occurring hydroxyl group at this position into a suitable leaving group, such as iodo, azido, 2-mesitylenesulfonyl and the like. Such compounds are readily prepared using conventional reagents and reaction conditions. For example, glucose-C6-2-mesitylenesulfonated vancomycin can be prepared by first protecting the free amino groups and the carboxylic acid with a suitable protecting group, such as allyloxycarbonyl (Aloc) groups for the free amino groups and an allyl ester for the carboxylic acid group. The glucose-C6 position can then be converted into a suitable leaving group, such as a 2-mesitylenesulfonyl group, using conventional reagents, such a 2-mesitylenesulfonyl chloride. Removal of the protecting groups using standard procedures then affords intermediates suitable for further derivatization. The preparation of suitable intermediates for use in this invention is described, for example, in WO 00/04044, published January 27, 2000, the disclosure of which is incorporated herein by reference in its entirety.

Subsequent displacement of the leaving group (i.e., 2-mesitylenesulfonyl group) from the glucose-C6 position with nucleophiles such as azide, thiols,

alcohols, and the like, then provides derivatives modified at the glucose-C6 position (i.e., *W* in formula I). Such reactions are typically conducted under conventional conditions, such as by treatment of glucose-C6-2-mesitylenesulfonated vancomycin with excess thiol, preferably 2 equivalents, in the presence of excess potassium carbonate. These reactions are typically conducted in an inert diluent, such as DMF, at a temperature ranging from 0°C to 100°C for 0.5 to 24 hours, or until the reaction is complete. When azide is used to displace the 2-mesitylenesulfonyl group, the resulting azido group can be reduced using standard reagents and conditions to afford the corresponding amino group. Optionally, this amino group can be further derivatized using conventional reactions, such as reductive alkylation, acylation and the like. After modification of the glucose-C6 position, the resulting intermediates may be further derivatized to afford compounds of this invention using the procedures described herein, i.e., by reductive alkylation. Alternatively, the glycopeptide may be derivatized first, i.e., by reductive alkylation, and then the glucose-C6 position modified using the procedures described herein.

Additional details and other methods for preparing the compounds of this invention are described in the Examples below.

Pharmaceutical Compositions

This invention also includes pharmaceutical composition containing the novel glycopeptide compounds of this invention. Accordingly, the glycopeptide compound, preferably in the form of a pharmaceutically acceptable salt, can be formulated for oral or parenteral administration for the therapeutic or prophylactic treatment of bacterial infections.

By way of illustration, the glycopeptide compound can be admixed with conventional pharmaceutical carriers and excipients and used in the form of aqueous solutions, tablets, capsules, elixirs, suspensions, syrups, wafers, and the like. Such pharmaceutical compositions will contain from about 0.1 to about 90% by weight of the active compound, and more generally from about 1 to about 30%. The pharmaceutical compositions may contain common carriers and excipients, such as

corn starch or gelatin, lactose, dextrose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride, and alginic acid. Disintegrators commonly used in the formulations of this invention include croscarmellose, microcrystalline cellulose, corn starch, sodium starch glycolate and alginic acid.

A liquid composition will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s), for example ethanol, glycerine, sorbitol, non-aqueous solvent such as polyethylene glycol, oils or water, with a suspending agent, preservative, surfactant, wetting agent, flavoring or coloring agent. Alternatively, a liquid formulation can be prepared from a reconstitutable powder.

For example a powder containing active compound, suspending agent, sucrose and a sweetener can be reconstituted with water to form a suspension; and a syrup can be prepared from a powder containing active ingredient, sucrose and a sweetener.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid compositions. Examples of such carriers include magnesium stearate, starch, lactose, sucrose, microcrystalline cellulose and binders, for example polyvinylpyrrolidone. The tablet can also be provided with a color film coating, or color included as part of the carrier(s). In addition, active compound can be formulated in a controlled release dosage form as a tablet comprising a hydrophilic or hydrophobic matrix.

A composition in the form of a capsule can be prepared using routine encapsulation procedures, for example by incorporation of active compound and excipients into a hard gelatin capsule. Alternatively, a semi-solid matrix of active compound and high molecular weight polyethylene glycol can be prepared and filled into a hard gelatin capsule; or a solution of active compound in polyethylene glycol or a suspension in edible oil, for example liquid paraffin or fractionated coconut oil can be prepared and filled into a soft gelatin capsule.

Tablet binders that can be included are acacia, methylcellulose, sodium carboxymethylcellulose, poly-vinylpyrrolidone (Povidone), hydroxypropyl

methylcellulose, sucrose, starch and ethylcellulose. Lubricants that can be used include magnesium stearate or other metallic stearates, stearic acid, silicone fluid, talc, waxes, oils and colloidal silica.

Flavoring agents such as peppermint, oil of wintergreen, cherry flavoring or the like can also be used. Additionally, it may be desirable to add a coloring agent to make the dosage form more attractive in appearance or to help identify the product.

The compounds of the invention and their pharmaceutically acceptable salts that are active when given parenterally can be formulated for intramuscular, intrathecal, or intravenous administration.

A typical composition for intra-muscular or intrathecal administration will consist of a suspension or solution of active ingredient in an oil, for example arachis oil or sesame oil. A typical composition for intravenous or intrathecal administration will consist of a sterile isotonic aqueous solution containing, for example active ingredient and dextrose or sodium chloride, or a mixture of dextrose and sodium chloride. Other examples are lactated Ringer's injection, lactated Ringer's plus dextrose injection, Normosol-M and dextrose, Isolyte E, acylated Ringer's injection, and the like. Optionally, a co-solvent, for example polyethylene glycol, a chelating agent, for example ethylenediamine tetracetic acid, and an anti-oxidant, for example, sodium metabisulphite may be included in the formulation. Alternatively, the solution can be freeze dried and then reconstituted with a suitable solvent just prior to administration.

The compounds of the invention and their pharmaceutically acceptable salts which are active on rectal administration can be formulated as suppositories. A typical suppository formulation will generally consist of active ingredient with a binding and/or lubricating agent such as a gelatin or cocoa butter or other low melting vegetable or synthetic wax or fat.

The compounds of this invention and their pharmaceutically acceptable salts which are active on topical administration can be formulated as transdermal compositions or transdermal delivery devices ("patches"). Such compositions include, for example, a backing, active compound reservoir, a control membrane,

liner and contact adhesive. Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.*, U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference in its entirety. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Preferably, the pharmaceutical compositions of this invention comprise a glycopeptide antibiotic and a cyclodextrin compound. Preferably, this pharmaceutical compositions are formulated for parenteral administration for the therapeutic or prophylactic treatment of bacterial infections.

By way of illustration, the glycopeptide antibiotic, preferably in the form a pharmaceutically acceptable salt, can be admixed with an aqueous cyclodextrin solution to form a composition of this invention. Such pharmaceutical compositions will typically contain from about 1 to about 40 weight percent of the cyclodextrin and a therapuetically effective amount of the glycopeptide antibiotic.

Preferably, the cyclodextrin employed in the pharmaceutical compositions of this invention is hydroxypropyl-β-cyclodextrin or sulfobutyl ether β-cyclodextrin. More preferably, the cyclodextrin is hydroxypropyl-β-cyclodextrin. Preferably, the cyclodextrin will comprise about 1 to 40 weight percent; preferably, about 2 to 30 weight percent; more preferable, about 5 to 15 weight percent, of the formulation.

Optionally, the pharmaceutical composition may contain other pharmaceutically acceptable components, such a buffers, surfactants, antioxidants, viscosity modifying agents, preservatives and the like. Each of these components is well-known in the art. See, for example, U.S. Patent No. 5,985,310.

Other components suitable for use in the formulations of the present invention can be found in *Remington's Pharmaceutical Sciences,* Mace Publishing Company, Philadelphia, PA, 17th ed. (1985). In a preferred embodiment, the aqueous cyclodextrin solution further compriese dextrose, preferably, about 5% dextrose.

The glycopeptide antibiotics used in this invention are effective over a wide dosage range and are typically administered in a theraputically effective amount. It, will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

Suitable doses are in the general range of from 0.01-100 mg/kg/day, preferably 0.1-50 mg/kg/day. For an average 70 kg human, this would amount to 0.7 mg to 7g per day, or preferably 7 mg to 3.5g per day.

The following formulation examples illustrate representative pharmaceutical compositions of the present invention.

Formulation Example A

This example illustrates the preparation of a representative pharmaceutical composition for oral administration of a compound of this invention:

Ingredients	Quantity per tablet, (mg)
Active Compound	200
Lactose, spray-dried	148
Magnesium stearate	2

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

Formulation Example B

This example illustrates the preparation of another representative pharmaceutical composition for oral administration of a compound of this invention:

Ingredients	Quantity per tablet, (mg)
Active Compound	400
Cornstarch	50
Lactose	145
Magnesium stearate	5

The above ingredients are mixed intimately and pressed into single scored tablets.

Formulation Example C

This example illustrates the preparation of a representative pharmaceutical composition for oral administration of a compound of this invention.

An oral suspension is prepared having the following composition.

Ingredients	
Active Compound	1.0 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.1 g
Granulated sugar	25.5 g
Sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 ml
Colorings	0.5 mg
Distilled water	q.s. to 100 mL

Formulation Example D

This example illustrates the preparation of a representative pharmaceutical composition containing a compound of this invention.

An injectable preparation buffered to a pH of 4 is prepared having the following composition:

Ingredients	
Active Compound	0.2 g
Sodium Acetate Buffer Solution (0.4 M)	2.0 mL
HCl (1N)	q.s. to pH 4
Water (distilled, sterile)	q.s. to 20 mL

Formulation Example E

This example illustrates the preparation of a representative pharmaceutical composition for injection of a compound of this invention.

A reconstituted solution is prepared by adding 20 mL of sterile water to 1 g of the compound of this invention. Before use, the solution is then diluted with 200 mL of an intravenous fluid that is compatible with the active compound. Such fluids are chosen from 5% dextrose solution, 0.9% sodium chloride, or a mixture of 5% dextrose and 0.9% sodium chloride. Other examples are lactated Ringer's injection, lactated Ringer's plus 5% dextrose injection, Normosol-M and 5% dextrose, Isolyte E, and acylated Ringer's injection

Formulation Example F

This example illustrates the preparation of a representative pharmaceutical composition for topical application of a compound of this invention.

Ingredients	grams
Active compound	0.2-10
Span 60	2
Tween 60	2
Mineral oil	5
Petrolatum	10
Methyl paraben	0.15
Propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
Water	q.s. to 100

All of the above ingredients, except water, are combined and heated to 60°C with stirring. A sufficient quantity of water at 60°C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. 100 g.

Formulation Example G

This example illustrates the preparation of a representative pharmaceutical composition containing a compound of this invention.

A suppository totaling 2.5 grams is prepared having the following composition:

Ingredients	
Active Compound	500 mg
Witepsol H-15*	balance

(*triglycerides of saturated vegetable fatty acid; a product of Riches-Nelson, Inc., New York, N.Y.)

Formulation Example H

An injectable preparation is prepared having the following composition:

Ingredients	
Active Compound (as free base equivalents)	9 mg
Hydroxypropyl-β-cyclodextrin	90 mg
Dextrose	33 mg
1 M NaOH	q.s. pH 4 to 5
Water for injection	q.s. to 1 mL

Hydroxypropyl-β-cyclodextrin and dextrose are dissolved in about 80% of the water for injection. The active compound is added and dissolved. pH is adjusted with 1 M NaOH to 4-5 and the volume is adjusted to 95% of the final volume with water for injection. The final pH check and adjustment are made and the volume is adjusted to final volume with water for injection. The formulation is sterile filtered

through 0.22 micron filter and filled under aseptic conditions into sterile vials. The vials are capped, labeled and stored frozen.

Formulation Example I

An injectable preparation is prepared having the following composition:

Ingredients	
Active Compound (as free base equivalents)	100 mg
Hydroxypropyl-β-cyclodextrin	200 mg
1 M NaOH	q.s. pH 4 to 5
Water for injection	q.s. to 1 mL

Hydroxypropyl-β-cyclodextrin is dissolved in about 60% of the water for injection. The active compound is added and dissolved. pH is adjusted with 1 M NaOH to 4.0-5.0 and the volume is adjusted to 95% of the final volume with water for injection. The final pH check and adjustment are made and the volume is adjusted to final volume with water for injection. The formulation is sterile filtered through 0.22 micron filter and filled under aseptic conditions into sterile vials and freeze-dried using an appropriate lyophilization cycle. Vials are capped (optionally under partial vacuum or dry nitrogen).

Utility

The glycopeptide compounds of this invention, and their pharmaceutically acceptable salts, are useful in medical treatments and exhibit biological activity, including antibacterial activity, which can be demonstrated in the tests described in the Examples. Such tests are well known to those skilled in the art, and are referenced and described in Lorian "Antibiotics in Laboratory Medicine", Fourth Edition, Williams and Wilkins (1991), which is hereby incorporated by reference.

Accordingly, this invention provides methods for treating infectious diseases, especially those caused by Gram-positive microorganisms, in animals. The compounds of this invention are particularly useful in treating infections caused by

methicillin-resistant staphylococci. Also, the compounds are useful in treating infection due to enterococci, including vancomycin-resistant enterococci (VRE). Examples of such diseases are severe staphylococcal infections, for example, staphylococcal endocarditis and staphylococcal septicemia. The animal may be either susceptible to, or infected with, the microorganism. The method comprises administering to the animal an amount of a compound of this invention which is effective for this purpose. In general, an effective amount of a compound of this invention is a dose between about 0.01 and about 100 mg/kg. A preferred dose is from about 0.1 to about 50 mg/kg of active compound. A typical daily dose for an adult human is from about 0.7 mg to about 7 g.

In practicing this method, the antibiotic can be administered in a single daily dose or in multiple doses per day. The treatment regimen may require administration over extended periods of time, for example, for several days or for from one to six weeks. The amount per administered dose or the total amount administered will depend on such factors as the nature and severity of the infection, the age and general health of the patient, the tolerance of the patient to the antibiotic and the microorganism or microorganisms in the infection.

Among other properties, the compounds of this invention are also expected to be more chemically stable compared to N-acyl glycopeptide derivatives.

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention.

EXAMPLES

In the examples below, the following abbreviations have the following meanings. Any abbreviations not defined have their generally accepted meaning. Unless otherwise stated, all temperatures are in degrees Celsius.

BOC, Boc	=	*tert*-butoxycarbonyl
DIBAL-H	=	diisobutylaluminum hydride
DIPEA	=	diisopropylethylamine
DMF	=	*N*,*N*-dimethylformamide
DMSO	=	dimethyl sulfoxide
eq.	=	equivalent
Et	=	ethyl
EtOAc	=	ethyl acetate
Fmoc	=	9-fluorenylmethoxycarbonyl
HOBT	=	1-hydroxybenzotriazole hydrate
Me	=	methyl
PyBOP	=	benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate
TEMPO	=	2,2,6,6-tetramethyl-piperidinyloxy, free radical
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TLC, tlc	=	thin layer chromatography

In the following example, vancomycin hydrochloride semi-hydrate was purchased from Alpharma, Inc. Fort Lee, NJ 07024 (Alpharma AS, Oslo Norway). Other reagents and reactants are available from Aldrich Chemical Co., Milwaukee, WI 53201.

General Procedure A
Reductive Alkylation of Vancomycin

To a mixture of vancomycin (1 eq.) and the desired aldehyde (1.3 eq.) in DMF was added DIPEA (2 eq.). The reaction was stirred at ambient temperature for 1-2 hours and monitored by reverse-phase HPLC. Methanol and $NaCNBH_3$ (1 eq.) were added to the solution, followed by TFA (3 eq.). Stirring was continued for an additional hour at ambient temperature. After the reaction was complete, the methanol was removed *in vacuo*. The residue was precipitated in acetonitrile. Filtration gave the crude product which was then purified by reverse-phase HPLC. If desired, other glycopeptides may be used in this procedure.

General Procedure B
Preparation of Amino-Substituted Aldehydes

A solution of an aminoacetal (1 eq), such as 2-aminoacetaldehyde dimethyl acetal, an aldehyde (1.05 eq), and $NaCNBH_3$ (1 eq) in CH_2Cl_2 is stirred at room temperature for 1-4 hours. The reaction is monitored by TLC. To the reaction mixture are added FmocCl(1 eq) and DIPEA (2 eq) at 0°C. Stirring is continued for 1-2 hours at room temperature. The reaction is then washed with 0.1 N HCl, water and brine. The solvent is removed *in vacuo* and the residue is purified by flash chromatography gave the amino-substituted acetal.

To the solution of above amino-substituted acetal in acetone is added 6 N HCl (1.5 eq). The reaction is stirred at room temperature for 5-16 hours. Solvent is removed *in vacuo* and the residue is dried under high vacuum to give crude amino-substituted aldehyde which is typically used without further purification.

General Procedure C
Preparation of Thio-Substituted Aldehydes

A solution of a bromoacetal (1 eq), such as dimethyl 2-bromoacetaldehyde, and sodium iodide (1 eq) in DMF is stirred at ambient temperature for 0.5 h. To the solution is added a substituted thiol (1 eq), such as *n*-decyl thiol, followed by potasium carbonate (1 eq). The mixture is stirred at 25-80°C for 4-16 hours. The reaction is then taken up with ethyl acetate, washed twice with water and once with sat. NaCl. The organic layer is dried over $MgSO_4$ and the solvent is removed *in vacuo*. Purification on flash chromatography (hexan: ethyl acetate = 8:1) provides the corresponding thio-substituted acetal.

To a solution of the thio-substituted acetal in acetone was added 6 N HCl (1.5 eq). The reaction is stirred at room temperature for 5-16 hours. The solvent is removed *in vacuo* and the residue is dried under high vacuum to give crude thio-substituted aldehyde which is typically used without further purification.

General Procedure D
Preparation of Thio-Substituted Aldehydes

A mixture of a thiol ester (1 eq), such as methyl thioglycolate, sodium iodide (1 eq), an alkyl bromide (1 eq) and potasium carbonate (1 eq) in DMF is stirred at room temperature for 4-16 hours. The reaction is taken up with ethyl acetate and washed with water and brine. The organic layer is dried over magnesium sulfate and solvent is removed *in vacuo*. Purification on flash chromatography provides the thio-substituted ester.

The thio-substituted ester in dry ether is treated with DIBAL-H (1 M solution in cyclohexane, 1.3 eq) at -78°C. The reaction is then stirred at -78°C for 2-4 hours. TLC is used to monitor the reaction progress. Upon completion, ethyl formate (0.5 eq) is added to quench the reaction. The reaction is then washed with 10% acetic acid, water and brine. The organic layer is dried over magnesium sulfate and the solvent removed to afford the crude thio-substituted aldehyde which is typically used without further purification.

General Procedure E
Preparation of Alkoxy-Substituted Aldehydes

A solution of a hydroxyacetal (1 eq), such as dimethyl 2-hydroxyacetaldehyde, in THF is treated with sodium hydride (1 eq) at 0°C. After hydrogen evolution ceases, an alkyl bromide is added at 0°C. The reaction is then stirred at room temperature for 1-4 hours. The reaction is taken up with ethyl acetate and washed with water and brine. The solvent is removed *in vacuo* and the residue typically purified by flash chromatography to afford the alkoxy-substituted acetal.

To a solution of the alkoxy-substituted acetal in acetone is added 6 N HCl (1.5 eq). The reaction is stirred at room temperature for 5-16 hours. The solvent is removed *in vacuo* and the residue is dried under high vacuum to give crude alkoxy-substituted aldehyde which is typically used without further purification.

General Procedure F
Preparation of Sulfonamido-Substituted Aldehydes

A solution of an aminoacetal (1 eq), such as dimethyl 2-aminoacetaldehyde, and diiospropylethylamine (2 eq) in THF is treated with a sulfonyl chloride (1 eq) at 0°C. The reaction is then stirred at room temperature for 1-4 hours. The reaction is then taken up with ethyl acetate and washed with 0.1 N HCl, water and brine. The solvent is removed *in vacuo* and the residue purified by flash chromatography gave the sulfonamido-substituted acetal.

To a solution of the sulfonamido-substituented acetal in acetone is added 6 N HCl (1.5 eq). The reaction is stirred at room temperature for 5-16 hours. The solvent is then removed *in vacuo* and the residue is dried under high vacuum to give crude sulfonamido-substituted aldehyde which is typically used without further purification.

Example A
Preparation of Fmoc-Aminoacetaldehyde

Fmoc-protected aminoethanol was prepared from aminoethanol by conventional techniques (e.g., as described in Examples B and C below).

To a mixture of Fmoc-aminoethanol (37.64g, 133 mmol, 1.0 equiv), TEMPO (0.008 M in CH_2Cl_2, 332.5 mL, 2.66 mmol, 0.02 equiv), KBr (0.5 M in water, 53.2 mL, 26.6 mmol, 0.2 equiv) and ethyl acetate (1,500 mL), at 0 °C, was added NaOCl (0.35 M, buffered to pH 8.6 by $NaHCO_3$, 760 mL, 266 mmol, 2.0 equiv). A mechanical stir was used to ensure efficient stirring, and the reaction was monitored by TLC. After 20 min, the two layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 250 mL), the combined organic layers were washed with saturated $Na_2S_2O_3$, water, and brine, dried over Na_2SO_4, filtered and concentrated to about 400 mL. Hexane (1,600 mL) was added to give a white precipitate. After filtration, Fmoc-aminoacetaldehyde (25.2g, 67%) was collected as a white powder.

Example B
Preparation of N-Fmoc-2-(n-Decylamino)acetaldehyde

To a solution of n-decanoyl chloride (2.7 mL, 13 mmol, 1.0 eq) in methylene chloride (20 mL) in an ice/acetone bath was added a mixture of glycine methyl ester hydrochloride (2.0 g, 16 mmol, 1.2 eq) and DIPEA (5.1 mL, 29 mmol, 2.2 eq) in methylene chloride (20 mL) dropwise. The reaction was stirred a further 60 min after complete addition, then washed with 3N hydrochloric acid (50 mL) twice, followed by saturated sodium bicarbonate (50 mL). The organics were dried over magnesium sulfate and the solvents removed under reduced pressure. Methyl 2-Decylamidoacetate (3.0 g, 12 mmol, 95%) was obtained which was used in the next step without further purification.

Under nitrogen, methyl 2-(n-decylamido)acetate (3.0 g, 12 mmol, 1.0 eq) was dissolved in anhydrous tetrahydrofuran (25 mL) and cooled in an ice bath. A solution of lithium aluminum hydride (1 N, 25 mL, 25 mmol, 2.0 eq) was added carefully. The resulting solution was refluxed under nitrogen overnight, then cooled in an ice bath. Tetrahydrofuran (50 mL) was added followed by slow addition of sodium sulfate decahydrate until effervescence ceased. The mixture was allowed to warm to room temperature, filtered, then concentrated under vacuum. 2-(n-Decylamino)ethanol (2.3 g, 11 mmol, 93%) was obtained which was used without further purification.

2-(n-Decylamino)ethanol (2.3 g, 11 mmol, 1.1 eq) and DIPEA (2.0 mL, 11 mmol, 1.1 eq) were dissolved in methylene chloride (15 mL) and cooled in an ice bath. 9-Fluorenylmethyl chloroformate (2.6 g, 10 mmol, 1.0 eq) in methylene chloride (15 mL) was added, the mixture stirred for 30 minutes then washed with 3N hydrochloric acid (50 mL) twice and saturated sodium bicarbonate (50 mL). The organics were dried over magnesium sulfate, and the solvents removed under reduced pressure. N-Fmoc-2-(decylamino)ethanol (4.6 g, 11 mmol, 108%) was used without further purification.

N-Fmoc-2-(n-Decylamino)ethanol (4.6 g, 11 mmol, 1.0 eq) and DIPEA (7.6 mL, 44 mmol, 4.0 eq) were dissolved in methylene chloride (30 mL) and cooled in an ice/acetone bath. A solution of sulfur trioxide pyridine complex (6.9 g, 43 mmol,

4.0 eq) in dimethyl sulfoxide (30 mL) was added, and the solution stirred for 20 minutes. Crushed ice was added and the mixture partitioned. The organics were washed with 3N hydrochloric acid twice, saturated sodium bicarbonate and saturated sodium chloride, dried over magnesium chloride, and concentrated under vacuum. N-Fmoc-2-(n-Decylamino)acetaldehyde (3.4 g, 8 mmol, 74%) was used without further purification.

Example C
Preparation of 2-(Decylamino)ethanol

A solution of aminoethanol (30.5 g, 500 mmol, 30.1 mL) and 1-bromodecane (27.65 g, 125 mmol, 26 mL) in ethanol was stirred at 65 °C for 4 hr. The solvent was removed under reduced pressure. The residue was diluted with EtOAc (800 mL) and the organic solution was washed with H_2O (2 x 200 mL); saturated aqueous $NaHCO_3$ (200 mL) and saturated brine (200 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude product, 2-(decylamino)ethanol, was used without further purification.

Example D
Preparation of N-Fmoc-2-(*trans*-Dec-4-en-1-ylamino)acetaldehyde

trans-4-Decenal (7.2 g, 46.6 mmol) was mixed with 40 mL (0.37 moL) of aminoacetaldehyde dimethylacetal in 400 mL of methanol and stirred at room temperature for 30 minutes. $NaCNBH_3$ (2.9 g, 46.6 mmol) was added, the reaction was cooled in an ice bath, and 27 mL (0.35 moL) of TFA was added dropwise over 5 minutes. The ice bath was then removed and the reaction was stirred for 70 minutes at room temperature, concentrated to a third of its volume, and partitioned between ethyl acetate (250 mL) and 1N NaOH (200 mL). The organic layer was washed with water (3 x 75 mL), dried over MgSO4 , filtered and concentrated under reduced pressure to yield 11.1 g (45.6 mmol) of 2-(*trans*-dec-4-en-1-ylamino)acetaldehyde dimethyl acetal as a yellow oil that was used directly in the next step.

2-(*trans*-Dec-4-en-1-ylamino)acetaldehyde dimethyl acetal (10.5 g, 43.2 mmol) was mixed with dichloromethane (300 mL) and 7.5 mL (43.2 mmol) diisopropylethyl amine and 11.2 g (43.2 mmol) of FMOC-Cl was added portionwise. The reaction was stirred at room temperature for 3 hours and then poured into a solution of 10% $KHSO_4$ (200 mL). The organic layer was washed with water (200 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting oil was chromatographed on silica gel in 10% EtOAc/Hexanes to give 16.1 g (34.6 mmol) of N-Fmoc-2-(*trans*-dec-4-en-1-ylamino)acetaldehyde dimethyl acetal as a clear oil that was used directly in the next step.

N-Fmoc-2-(*trans*-Dec-4-en-1-ylamino)acetaldehyde dimethyl acetal (5 g, 10.7 mmol) was mixed with 30 mL of TFA and stirred at room temperature for 30 minutes. The reaction was poured into water (140 mL) and centrifuged to obtain a clear oil. The supernatant was decanted and the oil was mixed with 40 mL of water and centrifuged again. The supernatant was again decanted and the oil was dissolved in dichloromethane (100 mL), dried over MgSO4, filtered, and concentrated under reduced pressure to obtain 5.2 g (12.3 mmol) of N-Fmoc-2-(*trans*-Dec-4-en-1-ylamino)acetaldehyde as a clear oil.

Example E

Preparation of a Compound of Formula V

(where R^{22} is OH and R^{23} is $-CH_2$-N-(N-CH_3-D-glucamine))

Vancomycin (9.0 g, 5.16 mmol) was added to a solution of N-methyl-D-glucamine (5.03 g, 25.8 mmol) and 37% formaldehyde (0.43 mL, 5.4 mmol) in 50% aqueous acetonitrile (60 mL) under nitrogen and stirred at room temperature. After 4 hours, the acetonitrile was removed in vacuo, water (30 mL) was added, and the pH was adjusted to ~4 with 10% trifluoroacetic acid. The solution was purified by reverse-phase HPLC. Fractions containing the desired product were identified by mass spectrometry, pooled, and lyophilized to give the title compound as a white powder. This intermediate may be further derivatized using the procedures described herein.

Example F
Preparation of a Compound of Formula IV
(where R^{15} and R^{16} are H, R^{22} is OH and R^{27} is $-CH_2CH_2$-NH-Fmoc)

Vancomycin hydrochloride (4.00 g, 2.60 mmol) was suspended in 40 mL of 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone and heated to 70°C for 15 minutes. *N*-(9-fluorenylmethoxycarbonyl)aminoacetaldehyde (720 mg, 2.6 mmol) was added and the mixture was heated at 70°C for one hour. Sodium cyanoborohydride (160 mg, 2.5 mmol) in 2 mL methanol was added and the mixture was heated at 70°C for 2 hours, then cooled to room temperature. The reaction solution was added dropwise to 20 mL of acetonitrile, giving a precipitate that was collected by centrifugation. The precipitate was purified by reverse-phase HPLC on a Ranin C18 Dynamax column (2.5 cm x 25 cm, 8μm particle size), at 10 mL/min flow rate using 0.045% TFA in water as buffer A and 0.045% TFA in acetonitrile as buffer B (HPLC gradient of 10-70% B over 90 minutes), which yielded the title intermediate as its trifluroacetate salt. MS calculated: MH^+, 1715; Found, 1715.

This compound can be deprotected and further derivatized, for example, via reductive alkylation, as described herein.

Example G
Synthesis of an Intermediate Compound of Formula III
(where *W* is OH, R^{15} is $-CH_2CH_2$-NH-$(CH_2)_9CH_3$, R^{17} is H and R^{22} is OH)

To an oven-dried, 1000 mL round bottomed flask, equipped with magnetic stirring bar, were added vancomycin (34.1 g, 23 mmol, 1 eq), N-Fmoc-aminoacetaldehyde (6.5 g, 23 mmol, 1eq), DIPEA (8.5 mL, 46 mmol, 2 eq) and DMF (340 mL). The mixture was stirred at ambient temperature over 2 hours, and monitored by HPLC. The reaction became homogenous, and ~90% conversion to the imine was observed. Methanol (340 mL) and $NaCNBH_3$ (4.3 g, 69 mmol, 3 eq) were added to the solution, followed by TFA (5.2 mL, 69 mmol, 3eq). Stirring was continued for an additional hour at ambient temperature. After the reaction was complete, methanol was removed *in vacuo*. The residue containing the crude product and DMF was slowly poured into a 5 L flask and stirred with acetonitrile (3.5 L). A white precipitate was formed. The suspension was allowed to settle at

ambient temperature and the supernetant was decanted. The white solid was filtered and triturated with ether (2 L). After filtration, the crude product was dried under high vacuum overnight.

An 8 x 26 cm column was packed with octadecyl bonded silical gel. The column was washed with 800 mL of 90% Solvent B [acetonitrile in water, 0.1% TFA] and equilibrated with 800 mL of 10% Solvent B. Crude product (10 g) was dissolved in 30% Solvent B (150 mL, containing 2 mL of 3 N HCl) and loaded onto the column. It was then flashed with 10%B (800 mL x 2), 40%B (800 mL x 3) and 90%B (800 mL). The fractions were checked by analytical HPLC. After lyophilization, N^{van}-Fmoc-aminoethyl vancomycin was obtained as its TFA salt.

N^{van}-Fmoc-aminoethyl vancomycin was deprotected to give N^{van}-aminoethyl vancomycin tri-TFA salt using conventional procedures (e.g. as described in Examples H and J)

To a solution of N^{van}-aminoethyl vancomycin tri-TFA salt (15.5 mg, 8.4 micromol) in methanol:DMF:THF (2:1:1, 1.6mL) was added decanal (92 microL, 59 micromol) and sodium cyanoborohydride (0.1M in methanol, 45 microL, 4.5 micromol). After 45 minutes, the solvents were removed in vacuo, and the residue purified by preperative HPLC. The appropriate fractions were combined and lyophylized to give N^{van}-2-(*n*-decylamino)ethyl vancomycin (2.4 mg) as a white powder. Also isolated was N^{van},N^{van}-bis-2-(*n*-decylamino)ethyl vancomycin (2.9mg).

Example H
Synthesis of an Intermediate Compound of Formula III
(where *W* is OH, R^{15} is $-CH_2CH_2-NH-(CH_2)_9CH_3$, R^{17} is H and R^{22} is OH)

Vancomycin hydrochloride (12 g, 7.7 mmol, 1.0 eq), N-Fmoc-2-(n-decylamino)acetaldehyde (3.2 g, 7.6 mmol, 1.0 eq) and DIPEA (2.6 mL, 14.9 mmol, 2.0 eq) were stirred at room temperature in DMF (120 mL) for 90 minutes. Sodium cyanoborohydride (1.4 g, 22 mmol, 3.0 eq) was added, followed by methanol (120 mL) then trifluoroacetic acid (1.8 mL, 23 mmol, 3.0 eq). The mixture was stirred for 60 minutes at room temperature, then the methanol removed under reduced pressure. The resulting solution was added to 600 mL diethyl ether giving a precipitate which

was filtered, washed with ether, and dried under vacuum. The crude product was purified on a reverse-phase flash column, eluting with 10, 20, 30% acetonitrile in water (containing 0.1% trifluoroacetic acid) to remove polar impurities (such as residual vancomycin) then the product was eluted with 70% acetonitrile in water (containing 0.1% trifluoroacetic acid) to give 9 g of N^{van}-(N-Fmoc-2-n-decylaminoethyl) vancomycin as its trifluoroacetate salt (4.3 mmol, 56%).

N^{van}-(N-Fmoc-2-n-decylaminoethyl) vancomycin (100 mg) was dissolved in 1 mL DMF (1 mL) and treated with piperidine (200 uL) for 30 minutes. The mixture was precipitated into ether, centrifuged and washed with acetonitrile. Reverse-phase preparative HPLC (10-70% acetonitrile in water containing 0.1% trifluoroacetic acid over 120 minutes) gave N^{van}-2-(*n*-decylamino)ethyl vancomycin as its TFA salt.

Example I

Synthesis of an Intermediate Compound of Formula III (where *W* is OH, R^{15} is $-CH_2CH_2-NH-(CH_2)_9CH_3$, R^{17} is H and R^{22} is -N-(D-glucosamine)

N^{van}-(N-Fmoc-2-n-decylaminoethyl) vancomycin (100 mg, 48 umol, 1.0 eq) was dissolved in 1 mL DMF and glucosamine hydrochloride was added (31 mg, 144 umol, 3.0 eq). The mixture was stirred vigorously for 30 minutes (the glucosamine hydrochloride did not fully dissolve), DIPEA (60 uL, 344 umol, 7.2 eq) was added and the mixture stirred vigorously for a further 30 minutes. A solution of benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP, 50 mg, 96 umol, 2.0 eq) and 1-hydroxybenzotriazole (14 mg, 104 umol, 2.2 eq) in 500 uL DMF was prepared. The PyBOP solution was added in 5 batches of 60 uL at intervals of 5 minutes to the vigorously stirred suspension of the other reaction components. The reaction was stirred an additional 30 minutes then precipitated into acetonitrile. The solid was collected by centrifugation, taken up in 1mL *N,N*-dimethylformamide and treated with 200 uL piperidine for 30 minutes. Precipitation into ether was followed by centrifugation and the solid washed with acetonitrile.

Reverse-phase preparative HPLC (10-70% acetonitrile in water containing 0.1% trifluoroacetic acid over 120 minutes) gave a compound of formula III where W is -OH; R^{15} is $-CH_2CH_2$-NH-$(CH_2)_9CH_3$ and R^{22} is -N-(D-glucosamine as its trifluoroacetate salt.

Example J
Synthesis of an Intermediate Compound of Formula III
(where W is OH, R^{15} is $-CH_2CH_2$-NH-$(CH_2)_9CH_3$ and R^{22} is -NH-CH(COOH)CH_2COOH)

HOBt (1.47 g, 10.9 mmol), PyBOP (7.57 g, 14.6 mmol), and the bis-fluorenylmethyl ester of L-aspartic acid (TFA, 6.26 g, 10.4 mmol) were added to a well stirred solution of N^{van}-(N-Fmoc-2-n-decylaminoethyl) vancomycin (20 g, 10.4 mmol) and DIPEA (5.44 mL, 31.2 mmol) in DMF (440 mL). The reaction was complete after 1 hr by MS. The mixture was precipitated into CH_3CN (4 L) and centrifuged. The supernatant was decanted and the pellet redissolved in DMF (440 mL). Piperidine (44 mL) was added and the reaction monitored by MS. After 1 hr reaction was complete. Precipitate via dropwise addition to Et_2O (4 L) with continued stirring overnight. The solid was collected via filtration and dried in vacuo. The resulting solid was then triturated with CH_3CN and collected via filtration and dried *in vacuo* giving desired product as an off-white solid which was purified by reverse phase HPLC.

Example K
Synthesis of an Intermediate Compound of Formula V
(where W is OH, R^{15} is H and R^{23} is $-CH_2$-NH-CH_2CH_2-NH-$(CH_2)_9CH_3$)

To 50% aqueous acetonitrile (1.0 mL) was added diaminoethane (30 mg, 0.5 mmol), 37% formalin (7.6 uL, 0.20 mmol) and vancomycin hydrochloride (140 mg, 0.10 mmol). After stirring for 3h, the product was precipitated by the addition of acetonitrile (12 mL). The solid was isolated by centrifugation, then washed with ether (12 mL). The resulting solid was dried in vacuo, and purified by reverse-phase HPLC (5-15%B over 40min at a flow rate of 50ml/min). Fractions containing the desired product were identified by mass spectrometry, pooled, and lyophilized to

give a compound of formula V where W is -OH and R^{23} is $-CH_2-NH-CH_2CH_2NH_2$ (85 mg) as a white powder. MS calculated (MH+), 1520; found, 1520.

To a solution of the compound from the above step (80 mg, 0.040 mmol) in ethanol (1.0 mL) and DMF (1.0 mL) was added n-decanal (6.3 mg, 0.040 mmol), and the mixture was stirred for 45 minutes. Sodium cyanoborohydride (0.1M in methanol, 400 uL, 0.040 mmol) was then added and the mixture stirred for 3 hours. The solvents were removed in vacuo, and the residue purified by preprative HPLC. Fractions containing the desired product were identified by mass spectrometry, pooled, and lyophilized to the title compound as a white powder. MS calculated (MH+), 1661; found, 1661.

Example L
Synthesis of an Intermediate Compound of Formula V (where W is OH, R^{15} is $-CH_2-NH-CH_2CH_2-NH-(CH_2)_9CH_3$ R^{22} is -N-(D-glucosamine) and R^{23} is $-CH_2-N-(N-CH_3-D-glucamine)$)

To 50% aqueous acetonitrile (10 mL) was added sequentially N-methyl-D-glucamine (975 mg, 5.0 mmol), 37% formalin (84 uL, 1.1 mmol), DIPEA (348 uL, 2.0 mmol) and N^{van}-(N-Fmoc-2-n-decylaminoethyl) vancomycin (2.15 g, 1.030 mmol). After stirring for 16h, the product was precipitated by the addition of acetonitrile (80 mL). The solid was isolated by centrifugation, then washed with acetonitrile (80 mL). The solid was dissolved in DMF (6.0 mL) and piperidine (2.0 mL). After 30 minutes, the product was precipated by the additon of acetonitrile (80 mL). The solid was isolated by centrifugation, then washed with ether (80 mL). The resulting solid was dried in vacuo, and purified by reverse-phase HPLC (10-35%B) over 40 min at a flow rate of 50 mL/min). Fractions containing the desired product were identified by mass spectrometry, pooled, and lyophilized to give a compound of formula V where W is -OH; R^{15} is $-CH_2-NH-CH_2CH_2-NH-(CH_2)_9CH_3$ and R^{23} is $-CH_2-N-(N-CH_3-D-glucamine$ (1.34 g) as a white powder. MS calculated (MH+), 1839; found, 1839.

The above compound (tetra TFA salt) (150 mg, 0.065 mmol) was dissolved in DMF. To this solution was added sequentially D-glucosamine hydrochloride (35

mg, 0.16 mmol), DIPEA (65 uL, 0.32 mmol), and a solution of PyBOP and HOBt in DMF (3.85 mL of a solution 0.02 M in each, 0.077 mmol each). After 30 minutes, the product was precipated by the additon of acetonitrile (40 mL). The solid was isolated by centrifugation, then washed with acetonitrile (40 mL). The resulting solid was dried in vacuo, and purified by reverse-phase HPLC (10-35%B over 40min at a flow rate of 50 mL/min). Fractions containing the desired product were identified by mass spectrometry, pooled, and lyophilized to the title compound as a white powder. MS calculated (MH+), 2000; found, 2000.

Example M
Synthesis of an Intermediate Compound of Formula IV
(where *W* is OH, R^{15} is $-CH_2-NH-CH_2CH_2-NH-(CH_2)_9CH_3$ R^{22} is -OH and R^{27} is $-CH_2C(O)OCH_2CH_3$)

A solution of vancomycin monohydrochloride (3.72 g, 2.5 mmol) in DMF (35 mL) was treated with diisopropylethylamine (0.87 mL, 5.0 mmol) followed by N-Fmoc-n-decylaminoacetaldehyde (1.05 g, 2.5 mmol). The resulting reaction mixture was stirred at room temperature for12 hours. Ethyl glyoxylate(2.5 mmol, 50% solution in toluene) was added and the reaction solution was stirred at 50 °C for 6 hours. The reaction mixture was cooled to room temperature and was treated with $NaCNBH_3$ (0.376 g, 6.0 mmol) followed by a solution of TFA (0.58 mL, 7.5 mmol) in MeOH (35 mL). After 20 min, MeOH was removed under reduced pressure and the crude was precipitated in acetonitrile (400 mL). The solid was collected by filtration. The crude was purified by preparative HPLC to give title compound. MS(M + H) 1939.2(M+, calculated 1938.7)

Example N
Synthesis of an Intermediate Compound of Formula IV
(where *W* is OH, R^{15} is $-CH_2-C(O)OCH_3$ R^{22} is -OH and R^{27} is $-CH_2C(O)OCH_3$)

A solution of vancomycin hydrochloride (7.43 g, 5.0 mmol) in DMSO (100 mL) was treated with diisopropylethylamine (1.74 mL, 10.0 mmol) followed by methyl bromoacetate (0.842 g, 5.5 mmol) at room temperature. The reaction mixture was stirred at room temperature overnight. The crude product was

precipitated using acetonitrile (1000 mL). The crude product was collected and purified by preparative HPLC to provide the title product. MS(M + H) 1522.0(M+, calculated 1519.45).

Example 1
Synthesis of a Compound of Formula III
(where *W* is NH_2, R^{15} is $-CH_2CH_2-NH-(CH_2)_9CH_3$, R^{17} is H and R^{22} is OH)

A solution of glucose C-6-azido vancomycin (109 mg, 74 μmol)(prepared as described in Example 26 of WO 00/04044) in DMF (1.0 mL) is treated with DIPEA (26 μL, 148 μmol) at room temperature followed by N-Fmoc-2-(n-decylamino)acetaldehyde (2.0 eq). The resulting reaction solution is stirred at room temperature for one hour. The mixture is then diluted with MeOH (1 mL), and treated with trifluoroacetic acid (17 μL, 3 eq) followed by sodium cyanoborohydride (3.0 eq). The reaction solution is stirred at room temperature for 30 min. and the volatile components are removed under reduced pressure. The crude product is poured into diethyl ether and the precipitate is collected and dried under vacuum. The resulting glucose C-6-azido N^{van}-(N-Fmoc-2-n-decylaminoethyl) vancomycin is used in the following reduction reaction without further purification.

A solution of glucose C-6-azido N^{van}-(N-Fmoc-2-n-decylaminoethyl) vancomycin in EtOH/H_2O/THF (1 mL/2 mL/4 mL) is treated with PMe_3 (0.5 mL) at room temperature. The resulting solution is stirred at room temperature overnight. The volatile components are removed under reduced pressure to afford glucose C-6-amino N^{van}-(N-Fmoc-2-n-decylaminoethyl) vancomycin.

Glucose C-6-amino N^{van}-(N-Fmoc-2-n-decylaminoethyl) vancomycin is dissolved in 1 mL DMF (1 mL) and treated with piperidine (200 uL) for 30 minutes. The mixture is precipitated into ether, centrifuged and washed with acetonitrile. If desired, the product is purified by reverse-phase preparative HPLC and the molecular weight determined by mass spectroscopy.

Example 2
Determination of Antibacterial Activity

A. *In Vitro* Determination of Antibacterial Activity

1. Determination of Minimal Inhibitory Concentrations (MICs)

Bacterial strains were obtained from either American Type Tissue Culture Collection (ATCC), Stanford University Hospital (SU), Kaiser Permanente Regional Laboratory in Berkeley (KPB), Massachusetts General Hospital (MGH), the Centers for Disease Control (CDC), the San Francisco Veterans' Administration Hospital (SFVA) or the University of California San Francisco Hospital (UCSF). Vancomycin resistant enterococci were phenotyped as Van A or Van B based on their sensitivity to teicoplanin. Some vancomycin resistant enterococci that had been genotyped as Van A, Van B, Van C1 or Van C2 were obtained from the Mayo Clinic.

Minimal inhibitory concentrations (MICs) were measured in a microdilution broth procedure under NCCLS guidelines. Routinely, the compounds were serially diluted into Mueller-Hinton broth in 96-well microtiter plates. Overnight cultures of bacterial strains were diluted based on absorbance at 600 nm so that the final concentration in each well was 5×10^5 cfu/mL. Plates were returned to a 35°C incubator. The following day (or 24 hours in the case of Enterococci strains), MICs were determined by visual inspection of the plates. Strains routinely tested in the initial screen included methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus*, methicillin-sensistive *Staphylococcus epidermidis* (MSSE), methicillin-resistant *Staphylococcus epidermidis* (MRSE), vancomycin sensitive *Enterococcus faecium* (VSE Fm), vancomycin sensitive *Enterococcus faecalis* (VSE Fs), vancomycin resistant *Enterococcus faecium* also resistant to teicoplanin (VRE Fm Van A), vancomycin resistant *Enterococcus faecium* sensistive to teicoplanin (VRE Fm Van B), vancomycin resistant *Enterococcus faecalis* also resistant to teicoplanin (VRE Fs Van A), vancomycin resistant *Enterococcus faecalis* sensitive to teicoplanin (VRE Fs Van B), enterococcus gallinarium of the Van A genotype (VRE Gm Van A), enterococcus gallinarium of the Van C-1 genotype (VRE Gm Van C-1), enterococcus

casseliflavus of the Van C-2 genotype (VRE Cs Van C-2), enterococcus flavescens of the Van C-2 genotype (VRE Fv Van C-2), and penicillin-sensitive Streptococcus pneumoniae (PSSP) and penicillin-resistant Streptococcus pneumoniae (PSRP). Because of the inability of PSSP and PSRP to grow well in Mueller-Hinton broth, MICs with those strains were determined using either TSA broth supplemented with defibrinated blood or blood agar plates. Compounds which had significant activity against the strains mentioned above were then tested for MIC values in a larger panel of clinical isolates including the species listed above as well as non-speciated coagulase negative *Staphylococcus* both sensitive and resistant to methicillin (MS-CNS and MR-CNS). In addition, they were tested for MICs against gram negative organisms, such as *Escherichia coli* and *Pseudomonas aeruginosa.*

2. Determination of Kill Time

Experiments to determine the time required to kill the bacteria were conducted as described in Lorian, "Antibiotics in Laboratory Medicine", Fourth Edition, Williams and Wilkins (1991), the disclosure of which is incorporated herein by reference in its entirety. These experiments were conducted normally with both staphylococcus and enterococcus strains.

Briefly, several colonies were selected from an agar plate and grown at 35°C under constant agitation until it achieved a turbidity of approximately 1.5 and 10^8 CFU/mL. The sample was then diluted to about 6 x 10^6 CFU/mL and incubated at 35°C under constant agitation was continued. At various times aliquots were removed and five ten-fold serial dilutions were performed. The pour plate method was used to determine the number of colony forming units (CFUs).

The compounds of this invention are active in the above tests *in vitro* tests and demonstrate a broad spectrum of activity.

B. *In Vivo* Determination of Antibacterial Activity

1. Acute Tolerability Studies in Mice

In these studies, a compound of this invention was administered either intravenously or subcutaneously and observed for 5-15 minutes. If there were no adverse effects, the dose was increased in a second group of mice. This dose

incrementation continued until mortality occurred, or the dose was maximized. Generally, dosing began at 20 mg/kg and increased by 20 mg/kg each time until the maximum tolerated dose (MTD) is achieved.

2. Bioavailability Studies in Mice

Mice were administered a compound of this invention either intravenously or subcutaneously at a therapeutic dose (in general, approximately 50 mg/kg). Groups of animals were placed in metabolic cages so that urine and feces could be collected for analysis. Groups of animals (n=3) were sacrificed at various times (10 min, 1 hour and 4 hours). Blood was collected by cardiac puncture and the following organs were harvested—lung, liver, heart, brain, kidney, and spleen. Tissues were weighed and prepared for HPLC analysis. HPLC analysis on the tissue homogenates and fluids was used to determine the concentration of the test compound or IiI present. Metabolic products resulting from changes to the test compound were also determined at this juncture.

3. Mouse Septecemia Model

In this model, an appropriately virulent strain of bacteria (most commonly S. aureus, or E. Faecalis or E. Faecium) was administered to mice (N=5 to 10 mice per group) intraperitoneally. The bacteria was combined with hog gastric mucin to enhance virulence. The dose of bacteria (normally 10^5-10^7) was that sufficient to induce mortality in all of the mice over a three day period. One hour after the bacteria was administered, a compound of this invention was administered in a single dose either IV or subcutaneously. Each dose was administered to groups of 5 to 10 mice, at doses that typically ranged from a maximum of about 20 mg/kg to a minimum of less than 1 mg/kg. A positive control (normally vancomycin with vancomycin sensitive strains) was administered in each experiment. The dose at which approximately 50% of the animals are saved was calculated from the results.

4. Neutropenic Thigh Model

In this model, antibacterial activity of a compound of this invention was evaluated against an appropriately virulent strain of bacteria (most commonly S. aureus, or E. Faecalis or E. Faecium, sensitive or resistant to vancomycin). Mice

were initially rendered neutropenic by administration of cyclophosphamide at 200 mg/kg on day 0 and day 2. On day 4 they were infected in the left anterior thigh by an IM injection of a single dose of bacteria. The mice were then administered the test compound one hour after the bacteria and at various later times (normally 1, 2.5, 4 and 24 hours) the mice were sacrificed (3 per time point) and the thigh excised, homogenized and the number of CFUs (colony forming units) were determined by plating. Blood was also plated to determine the CFUs in the blood.

5. Pharmacokinetic Studies

The rate at which a compound of this invention is removed from the blood can be determined in either rats or mice. In rats, the test animals were cannulated in the jugular vein. The test compound was administered via tail vein injection, and at various time points (normally 5, 15, 30,60 minutes and 2,4,6 and 24 hours) blood was withdrawn from the cannula In mice, the test compound was also administered via tail vein injection, and at various time points. Blood was normally obtained by cardiac puncture. The concentration of the remaining test compound was determined by HPLC.

The compounds of this invention are active in the above tests *in vivo* tests and demonstrate a broad spectrum of activity.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.